BEFORE THE

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
ORGANIZED PURSUANT TO THE
CALIFORNIA STEM CELL RESEARCH AND CURES ACT

IN RE:	)
	)
PUBLIC COMMENT ON CIRM'S STRATEGIC PLAN	)
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I N D E X

SAN FRANCISCO, CALIFORNIA; WEDNESDAY, MARCH 11, 2009

MR. SHEEHY: SO I WANT TO THANK EVERYBODY FOR COMING. MY NAME IS JEFF SHEEHY. I'M A MEMBER OF THE GOVERNING BOARD OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE. AND I'M NOT GOING TO WASTE A LOT OF TIME WITH INTRODUCTIONS. SO, ALAN, OUR PRESIDENT, ALAN TROUNSON, IS GOING TO START US OFF TODAY AND, AGAIN, ENGAGE, DISCUSS. ANY INPUT WE GET FROM YOU TODAY IS INCREDIBLY VALUABLE AS WE TRY TO FIGURE OUT WHERE WE'RE GOING INTO THE FUTURE WITH OUR STRATEGIC PLAN.

DR. TROUNSON: THANKS, JEFF. AND AS JEFF SAID, IT'S REALLY THE INPUT THAT WE'RE LOOKING FOR YOU. SO WHAT I'M GOING TO DO IS GIVE YOU A CONTEXT, AND THEN WE'RE REALLY GOING TO HAVE A REAL SCIENTIST -- I WISH I WAS A REAL SCIENTIST. MAGNIFICENT TIME, I THINK, TO BE A SCIENTIST -- GIVE US A TALK ABOUT HOW IT REALLY GOES FROM THE BENCH TO THE BEDSIDE, WHICH IS REALLY WHAT WE'RE ABOUT.

SO THE MISSION STATEMENT WHICH IS WHAT WE REALLY LOOK TO ALL THE TIME IN TRYING TO DEFINE HOW WE SET OUR PARAMETERS TO IS STATED HERE. AND REALLY WHAT IT'S SAYING, I THINK, AS I INTERPRET IT, IS THAT THE CALIFORNIA SEVEN MILLION PEOPLE WHO VOTED

IN FAVOR OF PROPOSITION 71 WANT TO SEE SOME OF THE DISCOVERIES TURNING INTO TREATMENTS IN THE CLINIC. IF THAT HAPPENS AT THE COMPLETION OF THE EXPENDITURE OF $3 BILLION, I THINK IT'S LIKELY TO BE CONSIDERED A WORTHWHILE EXPERIMENT. IF WE'VE GOT NOTHING REALLY IN THE CLINIC AT THAT TIME, I THINK THERE WOULD BE SOME CONCERNS BECAUSE THE GENERAL POPULATION IN CALIFORNIA WON'T UNDERSTAND THE VALUE OF *SCIENCE*, *CELL*, AND *NATURE* PAPERS AS US SCIENTISTS DO AS BEING THE PANACEA FOR WHAT WE DO, BUT ESSENTIALLY WHETHER THERE ARE ACTUALLY TREATMENTS PROGRESSING THROUGH THE CLINIC.

SO THERE ARE GOALS WHICH ARE FIVE- AND TEN-YEAR GOALS THAT WERE SET. I'VE JUST LISTED THEM HERE, AND THEY'RE IN THE HANDOUT. SO IT'S JUST TO REMIND EVERYBODY THAT THERE WERE TEN GOALS SET UP IN EACH OF THE FIVE-AND TEN-YEAR FRAMEWORKS. AND WE'VE BEEN SORT OF WORKING OUR WAY AS QUICKLY AS POSSIBLE TO COMPLETE THOSE.

THERE ARE SOME WHICH WE'VE BACKED OFF ON, AND GOAL NO. 5 THERE, ESTABLISHING A STEM CELL BANK, WE HADN'T ACTUALLY MADE ANY PROGRESS THERE. AND I THINK THAT WAS THE RIGHT THING IN RETROSPECT NOW, THAT THERE ARE STEM CELL BANKS ESTABLISHED HERE IN THE U.S. AND THROUGHOUT THE WORLD WHERE YOU CAN

ACCESS CELLS FROM A VERY MAJOR VARIETY OF DIFFERENT CELL TYPES, EMBRYONIC STEM CELLS AND ADULT STEM CELLS. BUT THE THINGS ARE CHANGING SO QUICKLY, THAT I THINK THAT THE BANKS IN THE END THAT WILL BE INCREDIBLY VALUABLE WILL BE THOSE ONES WHICH ARE ACCEPTED BY THE REGULATORY AUTHORITIES FOR CLINICAL APPLICATION.

SO IT MAY BE WHEN WE DO DO THE BANKING, IT'S GOING TO BE AT A DIFFERENT TIME THAN I THINK WAS FIRST ENVISAGED IN THE PLAN. MANY OF THE OTHER GOALS, AS YOU SEE IN ITALICS, WE'VE ADDRESSED OR ADDRESSING. AND ESSENTIALLY WE'RE ON THE MOVE TO DO THOSE THINGS. SO THESE GOALS HAVE REALLY NOT ALTERED PARTICULARLY. WHAT HAS CHANGED, OF COURSE, IS THE FRAMEWORK OVER WHICH WE'RE WORKING. AND THE TEN-YEAR GOALS HAVE BEEN WRITTEN IN A WAY WHERE YOU COULD PROBABLY MAKE THEM WITH ADJUSTMENTS, BUT WE DIDN'T HAVE IPS CELLS WHEN ALL OF THIS WAS WRITTEN CLEARLY. WE DIDN'T KNOW THAT WE WOULD BE PROGRESSING SO QUICKLY IN SOME OTHER AREAS.

AND SO THIS REVISION IS TO SORT OF REFORMAT THE STRATEGIC PLAN A LITTLE BECAUSE WE WERE REQUIRED TO RELOOK AT IT IN A FIVE-YEAR TIMEFRAME. AND WE'RE ABOUT TWO AND A HALF YEARS IN NOW. AND BECAUSE THINGS HAVE CHANGED SO QUICKLY AND BECAUSE

WE'VE MADE ADJUSTMENTS, WE THOUGHT IT WAS WORTHWHILE TRYING TO GET SOME INPUT FROM THE COMMUNITY AND FROM BUSINESS ABOUT WHAT SHOULD BE OUR PRIORITIES AND HOW SHOULD WE MAKE ADJUSTMENTS TO OUR CURRENT PLAN.

SO THOSE GOALS ARE THERE. PLEASE LOOK AT THEM. OFTEN PEOPLE DON'T READ THEM, BUT WE DO PAY ATTENTION TO THEM. THERE ARE SOME GOALS WHICH PROBABLY WILL TAKE SOME TIME TO ADJUST TO; FOR EXAMPLE, HOW WE GET INVOLVED WITH GMP FACILITIES. DO WE REALLY WANT TO BE OPERATING A FACILITY? DO WE WANT TO BE SUPPORTING THE OPERATION OF FACILITIES? SOME OF THOSE THINGS, I THINK, ARE STILL TO BE DETERMINED. WE'VE HAD WORKSHOPS ON THAT. AND MARIE CAN ADDRESS THOSE QUESTIONS IF YOU HAVE IN THAT AREA.

SO WE DO SEE IT AS A PIPELINE AND A VALUED PIPELINE AT THAT. SO WE UNDERSTAND THAT THE BASIC AND DISCOVERY RESEARCH WILL USUALLY ALL BE DONE IN THE UNIVERSITIES, RESEARCH INSTITUTES, AND HOSPITALS. IT DOES HAPPEN IN COMPANIES AND PARTICULARLY IN DRUG COMPANIES. SOME VERY SPECIAL DEVELOPMENTS DO OCCUR, BUT GENERALLY THE BASIC CHANGES IN DISCOVERY ARE HAPPENING DOWN THAT END IN THE NOT-FOR-PROFIT INSTITUTIONS. THEN THERE'S AN AREA WHERE IT REQUIRES VENTURE TO COME IN NORMALLY

TO SUPPORT THE TRANSLATIONAL WORK WHERE THE BIOTECH COMPANIES, THE BIOTECHNOLOGY COMPANIES, ARE VERY SOUND IN THE WAY THEY DO THOSE THINGS. THEY'VE HAD EXPERIENCE. THEY KNOW WHAT'S REQUIRED FOR MEETING THE RISK AND EFFICACY REQUIREMENTS BY THE REGULATORY AGENCIES AND THEN AT THE OTHER END WHERE THE BIG BIO OR THE PHARMACEUTICAL COMPANIES WILL BE MOST ACTIVE.

NOW, EACH ONE OF THESE DEVELOPMENTS WILL BE ITSELF DIFFERENT, BUT WE UNDERSTAND IN PRINCIPLE THAT IT WORKS LIKE THIS. THE COSTS CHANGE ALSO QUITE DRAMATICALLY FROM ONE END WHERE DEVELOPMENT OF A DISCOVERY MAYBE COSTS A MILLION OR $5 MILLION, BUT THE BY THE TIME YOU GET IT THROUGH TO THE CLINICAL END AND OUT TO THE COMMUNITY, IT CAN COST UP TO A BILLION DOLLARS IN THE PHARMACEUTICAL MODEL OR EVEN MULTIPLE BILLION DOLLARS TO GET ALL THOSE DRUGS THROUGH EACH ONE OF THEM.

SO IT'S GOING TO COST A LOT OF MONEY AT SOME POINT IN TIME AS WE TAKE THERAPIES AND DRUGS WHICH ARE EMANATING FROM THERAPIES THROUGH. SO WE'RE GOING TO HAVE TO LOOK AT SOME WAYS OF HELPING TO HELP THE SYSTEM WORK IN THIS. THE PHARMACEUTICAL COMPANIES COME IN AND TAKE A PIECE, WHETHER THEY WILL REALLY TAKE ENOUGH OF THE WHOLE TO ACCOMMODATE ALL OF THE NEEDS OF THE COMMUNITY WE'RE VERY

DOUBTFUL ABOUT. SO WE THINK THAT THERE MIGHT NEED TO BE A CHANGE IN THE CONSIDERATION OF HOW TO FUND CLINICAL TRIALS. AND IT MAY BE THAT WE HAVE TO TALK GOVERNMENT INTO BEING INVOLVED IN THAT END BECAUSE THEY WOULD BE THE BENEFICIARIES IF CURES HAPPEN AND ALSO TALKING THE HEALTH INSURANCE COMPANIES TO BE INVOLVED.

SO THIS IS ONE OF THE AREAS WHERE WE THINK THERE'S A POTENTIAL ROADBLOCK WHICH WE NEED TO ADDRESS, AND IT'S ONE OF THE AREAS THAT WE THINK WE OUGHT TO BECOME ACTIVE IN, HOW TO FIGURE OUT HOW TO FUND THOSE CLINICAL TRIALS BECAUSE WE WOULDN'T REALLY HAVE THE MONEY TO RUN ALL OF THOSE, CERTAINLY NOT RUN MANY OF THEM.

MOVING THE PIPELINE FORWARD IS SHOWING YOU HERE IN THE GREEN IS THE BASIC AREAS, AND THAT'S WHAT WE'VE BEEN FUNDING UP UNTIL NOW. THE GREEN COMPONENTS ARE THERE, THE SEED, COMPREHENSIVE, NEW FACULTY AWARDS, ETC., THE BIOLOGY OF STEM CELLS, THESE ARE ALL AT THE BASIC END OF THE FRAMEWORK. WE'RE NOW ONLY JUST MOVING INTO TRANSLATION. WE HAVE AN EARLY TRANSLATIONAL RFA WHICH HAS BEEN UNDER REVIEW, HAS BEEN THROUGH REVIEW. THE DISEASE TEAM PROGRAM WHERE WE'RE SEEKING TEAMS TO INPUT TO TAKE DISCOVERIES THROUGH TO AN IND WITHIN FOUR YEARS,

QUITE DEMANDING, BUT WE UNDERSTAND THERE ARE A LOT OF TEAMS OUT THERE THAT BELIEVE THAT THEY'RE IN THIS FRAMEWORK, UP TO A HUNDRED OR MAYBE EVEN MORE.

AND THAT WAS SURPRISING TO US THAT THERE ARE THAT MANY; AND IF THERE ARE, THERE'S SOME REASON WHY THEY'RE NOT SORT OF PROGRESSING MORE QUICKLY.

WE THINK THAT IF YOU'RE GOING TO USE STEM CELLS, YOU HAVE TO ADDRESS THE IMMUNOLOGY BECAUSE IF THEY'RE ALLOGENEIC TO THE PATIENT, IF THEY'RE DIFFERENT TO THE PATIENT, THEN WE ARE GOING TO HAVE TO ADDRESS THE ISSUE OF REJECTION. AND SO TOLERANCE OR TOLERANCE TO TRANSPLANTATION IS GOING TO BE A KEY, AND WE WANT TO DO SOMETHING ABOUT THAT. SO THAT FITS IN PRETTY MUCH BETWEEN THE BASIC AND THE CLINICAL COMPONENT, DEVELOP METHODOLOGIES THAT ALLOW WHEN WE TRANSPLANT CELLS, THAT THEY'LL REMAIN -- THEY'LL CONTINUE TO DO THE JOB WHICH THEY'RE INTENDED TO DO.

THE AWARDS FUNDED TO DATE BY THE ICOC, THERE'S BEEN OVER $630 MILLION ALLOCATED AND SHOWN IN THAT PIE CHART WHERE IT'S GONE IN TERMS OF TRAINING, RESEARCH GRANTS, SHARED LABORATORIES, AND FACILITIES. SO IT'S A BIG CHUNK OF MONEY THAT WE'VE INVESTED IN CALIFORNIA.

AND IF YOU LOOK AT WHAT THE EXTENT OF

FUNDS THAT HAVE BEEN ACTUALLY AGREED TO BY THE ICOC, WHICH INCLUDES AROUND 200 MILLION FOR THE DISEASE TEAMS, WE'RE GETTING UP TO AROUND ONE BILLION OR ABOUT A THIRD OF THE ENTIRE $3 BILLION PROGRAM. SO IT IS AN IMPORTANT STAGE, I THINK, TO SORT OF CHECK WITH THE COMMUNITY THAT WE'RE PROGRESSING IN THE RIGHT DIRECTION AND WE'RE SEEING THE PRIORITIES REFLECTED FROM WHAT YOU THINK THEY ARE.

THE DISTRIBUTION ACCORDING TO THE DIFFERENT PROGRAMS, ESSENTIALLY MOST OF THE BASIC RESEARCH REQUIRES LESS MONEY FOR EACH OF THE PROJECTS THAN DOES THE TRANSLATION. WE ASKED THE ICOC FOR $60 MILLION FOR THAT PROGRAM, AND WE ASKED FOR $210 MILLION FOR THE DISEASE TEAMS. YOU CAN SEE BY THIS PIE CHART THAT THAT'S A MUCH MORE EXPENSIVE COMPONENT THAN THE BASIC SCIENCE AREAS. SO IT'S REFLECTED IN THE NEEDS, THE NEEDS FOR ANIMAL MODELS DOING VOLUMES OF WORK GETTING MANUFACTURING INTO PLACE AND SO ON. THESE KIND OF THINGS TEND TO BE MORE EXPENSIVE UNFORTUNATELY THAN WOULD BE THE BASIC RESEARCH. SO THE SHIFT, IF YOU LIKE, FOR US MOVING INTO THIS TRANSLATION EARLY CLINICAL PHASES IS THAT THERE WILL BE MORE MONEY EXPENDED IN THOSE PROGRAMS THAN THERE IS IN THE BASIC PROGRAMS.

THE AVERAGE AWARDS, JUST TO SHOW YOU, ARE

IN THE UPPER REACHES OF NIH GRANTS. SO WE TEND TO FUND ON THE UPPER SIDE OF VALUE REALLY BECAUSE WE WANT THE PROJECTS DONE. WE DON'T WANT TO CUT ANYTHING BACK. WE'VE ALWAYS RESISTED ANY PRUNING OF THE BUDGETS. WE TAKE THE BUDGETS THAT ARE SUBMITTED EXCEPT WHERE IT DOES SEEM STRANGE WHERE WE GO BACK TO THE APPLICANT AND CHECK ON IT, BUT WE'VE NOT GONE ON 10-PERCENT PRUNING OR 20-PERCENT PRUNING TO IMPROVE THE PROGRAM. WE'VE SAID, OKAY, THAT'S THE MONEY THAT'S REQUIRED TO DO THE JOB. LET'S DO IT.

AND I THINK FROM MY OWN POINT OF VIEW WHEN I WAS WORKING ON IT, ONE OF THE THINGS THAT EVERY TIME HAPPENED TO ME WAS THAT THEY CUT BACK 10 PERCENT OR 20 PERCENT IN THE PROJECT, AND IT JUST MADE IT SO MUCH HARDER TO DO IT. IN FACT, WE OFTEN DIDN'T DO PART OF IT BECAUSE THE MONEY WOULDN'T REACH THAT DISTANCE.

THE STEM CELL PATHWAYS, THE BASIC SIDE OF IT, THE RENEWAL, THE DEVELOPMENT OF PLURIPOTENTIAL STEM CELLS, AND THEN THE DIFFERENTIATION OUT INTO THE PRIMARY LINEAGES OF MESODERM, ENDODERM, AND ECTODERM, THEY'RE THE PRIMARY GERM LINEAGES. AND THE DIFFERENTIATION PROGRAMS ARE MOVING REALLY QUITE QUICKLY, AND THEY'RE STARTING TO SETTLE DOWN INTO SOME REALLY ACCEPTABLE DIFFERENTIATION PATHWAYS, AND

IT'S GIVING US OPPORTUNITIES TO DO A LOT OF DIFFERENT THINGS, INCLUDING TISSUE ENGINEERING. WE'RE STARTING TO GROW THE CELLS IN ASSOCIATION WITH SCAFFOLDS. WE'RE LOOKING TOWARDS THE CELL THERAPIES IN ANIMAL MODELS AND TRANSPLANTATION AND, HENCE, IMMUNOLOGY IS BECOMING IMPORTANT THERE.

THE OPPORTUNITY FOR DRUG DISCOVERY IS RAPIDLY COMING TO THE FORE, PARTICULARLY WITH SOME OF THE LARGE ENTITIES WHO USE HIGH THROUGHPUT TECHNOLOGIES IN A VERY MAJOR WAY. THERE ARE A LOT OF MOLECULES THAT HAVE BEEN IDENTIFIED THAT COULD DO THE JOBS THAT WE THINK THAT THE CELLS MIGHT DO. SO THERE'S A LOT OF INTERESTING DRUGS COMING THROUGH THAT PIPELINE THAT TEND TO MORE FIT INTO THE DRUG DISCOVERY MODEL, BUT THEY'RE COMING ON BOARD VERY QUICKLY.

WE HAVE THE OPPORTUNITY OF LOOKING AT ENVIRONMENTAL TOXICOLOGY USING LIVER CELLS AND HEART CELLS AND ALSO THE POSSIBILITY OF DELIVERING GENE THERAPIES USING CELLS AS VEHICLES RATHER THAN VIRAL CONSTRUCTS. SO THERE'S A LOT OF OPPORTUNITY HERE.

WHAT ARE THE PRIMARY TARGETS FOR US AT THE MOMENT? WE SEE THEM IN THIS KIND OF FLOW HERE, THAT THE BASIC DISCOVERY IN STEM CELL BIOLOGY WILL REMAIN ALWAYS IMPORTANT TO US. TOOLS AND TECHNOLOGIES TO

DRIVE BASIC RESEARCH AND TRANSLATION, NEW MOLECULES AND THERAPEUTIC APPLICATIONS BASED ON STEM CELL RESEARCH, SO WE'RE INTERESTED IN THAT AND PROMOTING IT, BRINGING IT THROUGH TO THE CLINIC. MOBILIZATION OF ENDOGENOUS STEM CELLS FOR TISSUE REPAIR. I THINK THERE'S A GOOD CASE STILL FOR MOLECULES THERE THAT CAN RELEASE CELLS FROM THEIR STEM CELL STATE. IDENTIFICATION OF ABERRANT STEM CELLS, SUCH AS CANCER STEM CELLS, CELL THERAPIES, OF COURSE, GENE THERAPIES, AND TISSUE RECONSTRUCTION.

WHAT TO EXPECT. EVERYONE WILL HAVE A DIFFERENT LIST, BUT I CLEARLY THINK THERE WILL BE NEW MOLECULES, AND THEY'RE ALREADY COMING INTO IND'S THAT WILL HAVE AN INFLUENCE, HOPEFULLY PREVENT CANCERS, ENABLE EX VIVO STEM CELL EXPANSION AND DIFFERENTIATION AND TOLERANCE. THESE MOLECULES ARE APPEARING ALREADY. SPINAL CORD REPAIR, WE HAVE A CLINICAL TRIAL NOW FOR HUMAN EMBRYONIC STEM CELL-DERIVED CELLS. RETINAL EPITHELIAL REPAIR I THINK IS VERY MUCH ON THE HORIZON. I EXPECT A NUMBER OF THOSE GRANTS TO APPEAR IN THE DISEASE TEAMS.

BETA ISLET CELLS FOR DIABETICS, CERTAINLY A LOT OF EFFORT GOING IN THERE. CARDIAC MUSCLE CELLS AND PROGENITORS, THE CELLS THEMSELVES OR AS

PATCH SCAFFOLDS. VERY INTERESTING TECHNOLOGY THAT'S STARTING TO COME OUT. NEURAL STEM CELLS, FOR EXAMPLE, LYSOSOMAL STORAGE DISEASES OR THE MYELIN REPLACING OLIGODENDROCYTE-TYPE CELLS, THEY'RE GOING TO APPEAR. TARGETING OF METASTATIC CANCER CELLS, WE HOPE THAT WE'LL END UP WITH MOLECULES AND ANTIBODIES THAT WILL TARGET THESE CELLS BASED ON STEM CELL EXPERIMENTS. AND BECAUSE I USED TO WORK IN THE AREA, I BELIEVE THE LUNG IS A GREAT TARGET FOR STEM CELLS. SO REPAIR OF INFLAMMATORY LUNG FIBROSIS, I THINK, WILL ALSO BE EARLY IN THE CLINIC.

SO IF YOU LOOK AT WHAT CAN BE ACHIEVED FROM THESE PLURIPOTENTIAL STEM CELLS OR FROM PROGENITOR CELLS THAT YOU CAN FIND IN THE PATHWAYS OR REFORMATTED ADULT STEM CELLS THAT MAY HAVE ONLY BEEN DRIVEN BACK PART OF THE WAY OR ALL THE WAY BACK TO PLURIPOTENTIALITY, WE'RE GOING TO HAVE CELL THERAPIES COMING. STEM CELL MOBILIZATION OF SMALL MOLECULES, IT'S THERE. I THINK THE REVOLUTION IS NOW ON. I THINK THEY'RE GOING TO APPEAR IN THE CLINIC, AND I THINK CIRM OUGHT TO BE PART OF THE VEHICLE IN DELIVERING THAT.

SO OUR KIND OF PROVISIONAL PROGRAMS, LOOK AT SOME OF THOSE HERE AT THE BOTTOM WHERE I'VE GOT THAT BENT ARROW, WILL BE THE PROGRAMS WHICH WILL

ROTATE ON A 12- TO 18-MONTH BASIS. SO THESE ARE THE SO-CALLED CORE PROGRAMS: EARLY TRANSLATION, DISEASE TEAMS, AND BASIC SCIENCE, THAT THEY WILL CONTINUE TO DO THOSE. AND WE'LL ALSO THEN HAVE MULTIPLES WHERE NECESSARY. TOOLS AND TECHNOLOGIES, TRAINING GRANTS, AND THE TYPE OF BRIDGES PROGRAMS TO BRING TECHNICIANS THROUGH FROM THE CALIFORNIA COLLEGE SYSTEM INTO THE AREA.

SO IF YOU SEE IT LIKE THAT, THEN THAT'S THE WAY WE ARE HOPING TO FORMAT IT. IMMUNOLOGY IS SHOWN THERE AS A SPECIAL ONCE-OFF PROGRAM. WE MAY NEED TO DO MULTIPLES OF THAT, BUT WE SEE IT'S IMPORTANT TO HIT THINGS WHICH ARE A DEFICIT IN THE SYSTEM, A ROADBLOCK, IF YOU LIKE. AND IT'S THE WAY WE'RE SEEING IT.

NOW, THAT'S A VERY DIFFERENT WAY WE'RE LOOKING AT OUR PROGRAM THAN THE WAY WE HAD IT. WE WOULD HAVE BEEN EXPECTED TO DO 12 TO 15 RFA'S A YEAR. AND I CAN SEE MARIE SHAKING HER HEAD. IT'S JUST NOT POSSIBLE TO DO THAT IF WE WERE STICKING TO THE ORIGINAL PLAN. WE WANT A MORE COHERENT PLAN. WE WANT PEOPLE TO UNDERSTAND WHAT OUR PLAN IS AND BE ABLE TO PLAN THEMSELVES AS SCIENTISTS OR AS COMPANIES FOR COMING INTO OUR PROGRAMS. SO THAT'S AN IMPORTANT COMPONENT.

WHERE DO WE REALLY FIT? AND IT'S A GOOD QUESTION THAT WE'VE BEEN ASKING THE COMPANIES. WE'VE ASKED THE LAST PUBLIC SESSION THAT WE HAD IN LOS ANGELES. WHAT'S REALLY HAPPENING HERE NOW THAT THE PRESIDENT HAS REALLY MADE HIS PROCLAMATION TO REMOVE THE NEGATIVITY THAT WAS IN THE BUSH ADMINISTRATION ABOUT EMBRYONIC STEM CELLS? WE EXPECT NIH TO COME INTO THE BASIC END IN A MUCH MORE FULSOME WAY. WE EXPECT MORE FUNDING TO COME INTO THAT END.

I ALSO THINK, BECAUSE I SPENT A LOT OF TIME TALKING TO MANY INDIVIDUALS IN THE PHRMA AND THE BIOTECH SECTOR, THAT THE PHARMACEUTICAL INDUSTRY IS BACKING UP TO THIS AREA. THEY'VE ALL GOT REGENERATIVE MEDICINE COMPONENTS, AND THEY'VE EVEN GOT CELL THERAPIES, MOST OF THEM HAVE GOT CELL THERAPY COMPONENTS. THEY'RE INTERESTED. THEY PROBABLY WILL DO IT BY MAKING TRADE BUY-INS AND BUYING SOME OF THE BIOTECH COMPANIES THAT ARE SUCCESSFUL. THEY'RE BACKING INTO THIS END.

WOULDN'T OUR NATURAL NICHE BE SOMEWHERE BETWEEN THE BASIC SCIENCE AND THE CLINIC BECAUSE THIS SO-CALLED VALLEY OF DEATH OR VALLEY OF OPPORTUNITY, WHICHEVER WAY YOU WANT TO PUT IT, IS SOMETHING THAT WE COULD ACTUALLY -- WE COULD BE THE

CONDUIT FOR CONNECTING THE TWO ENDS. I THINK THAT THAT'S WHERE WE SHOULD BE. I THINK IT'S A NATURAL NICHE FOR US. IT'S NOT THAT WE WANT TO GO OUT OF THE BASIC OR, IN FACT, NOT DO ANY CLINICAL, BUT WE REALLY WANT TO SEE IF WE CAN MAKE THIS DISCOVERY GO THROUGH TO THE CLINIC. IF WE CAN DO THAT, THEN THAT'S PRIMARY TO OUR MISSION. SO WE'D BE INTERESTED IN WHAT YOU THINK ABOUT THAT.

THERE ARE INTERESTING NEW SYSTEMS COMING INTO PLAY. THE HIGH THROUGHPUT SCREENS FOR SMALL MOLECULES ARE REALLY NOW STARTING TO COUNT BECAUSE THEY'RE ALL USING THE STEM CELL ASSAYS THAT THE BASIC SCIENTISTS HAVE WORKED OUT. SO NOW YOU CAN SEE QUICKLY THAT THOSE ASSAYS ARE MOVING INTO THE HIGH THROUGHPUT SCREENS, AND LOTS OF MOLECULES WILL START TO PERCOLATE OUT.

BUT THERE ARE NEW NOVEL MODEL SYSTEMS. THERE'S PERSONALIZED MEDICINE OPPORTUNITIES FROM IPS CELLS. THE RECENT DEMONSTRATION THAT YOU CAN EXCISE ALL YOUR CONSTRUCT FROM IPS CELLS MEANS THAT THEY COULD BE USED CLINICALLY, I THINK, IN THE FUTURE. I DON'T THINK THERE'S MUCH DOUBT ABOUT THAT. THINGS HAVE CHANGED. BUT THE OPPORTUNITY IS GRAND, AND I THINK IT'S WHAT WE SHOULD BE DOING. AND THAT'S WHY WE'VE SORT OF DECIDED TO GET SOMEONE LIKE ARNOLD

KRIEGSTEIN TO GIVE YOU A VIEW OF HOW IT IS TO GO FROM THE BASIC END TO THE CLINIC BECAUSE HE'S DONE IT. HE'S ONE OF THOSE SCIENTISTS THAT'S GONE THAT DISTANCE AND KNOWS WHAT THE PITFALLS AND DIFFICULTIES ARE.

JUST IN MY LAST SLIDE, JEFF, IS TO NOTE THAT WE'VE MADE SOME AGREEMENTS WITH COUNTRIES OVERSEAS SHOWN HERE AS CANADA, JAPAN, SPAIN, UK, AND VICTORIA FOR COLLABORATIVE GRANTING OF PROJECTS. SO IF THE SCIENTISTS COME TOGETHER FROM THOSE COUNTRIES AND CALIFORNIA, THOSE COUNTRIES WILL FUND THEIR COMPONENT AND WE WILL FUND THE CALIFORNIA COMPONENT. WE ALREADY HAVE ONE GOING WITH THE VICTORIANS IN THE EARLY TRANSLATIONAL PROGRAMS. I THINK WE HAVE TO SAY THAT IT WAS REALLY INTERESTING. I CAN'T TELL HOW WELL IT WENT, BUT I THINK IT WAS INCREDIBLY INTERESTING.

I THINK THERE'S AN OPPORTUNITY TO GATHER THE REST OF THE WORLD AND NOW THE U.S. THROUGH THE NIH AND THE FDA FOR A REALLY CONCERTED GLOBAL EFFORT TO CHALLENGE THESE HUGE DISEASES, THESE MASSIVE PROBLEMS WITH A NEW TYPE OF MEDICINE. AND WHY NOT? WHY NOT US GIVE IT A REAL GO? AND SO INSTEAD OF DUPLICATING WHAT OUR COLLEAGUES ARE DOING OVERSEAS, LINK ARMS WITH THEM AND SEE IF WE CAN MAKE IT HAPPEN

MORE EFFECTIVELY AND MORE EFFICIENTLY. THAT'S WHAT WE HOPE.

NOW, IF I MAY, JEFF, I COULD HAND OVER TO ARNOLD TO GIVE YOU WHAT REALLY IS THE GENUINE EXPERIENCE OF SOMEONE WHO'S TAKEN IT FOR THE RUN-THROUGH FROM THE BASIC TO THE CLINICAL.

DR. KRIEGSTEIN: SO FIRST I WANT TO THANK ALAN FOR INVITING ME. I CERTAINLY APPRECIATE THE OPPORTUNITY TO TALK HERE TODAY. HOWEVER, I'D LIKE TO ALTER A LITTLE BIT MY COMMENTS TO ADDRESS WHAT I THINK IS THE REAL PURPOSE OF THIS MEETING, WHICH ARE THE STRATEGIC PLANS FOR THE CIRM, HOW THEY PROPOSE TO FUND THIS EFFORT IN THE NEXT FIVE OR EIGHT YEARS, WHATEVER THE REST OF OUR PERIOD MIGHT BE, AND MAKE SOME COMMENTS ABOUT WHAT I CONSIDER ARE CAUTIONS IN TERMS OF AREAS THAT PROBABLY DO, IN FACT, MERIT INVESTIGATION AND FUNDING AND THE NEED TO BE PUSHED AND PURSUED AND OTHER AREAS THAT I THINK MAYBE WE SHOULD RECONSIDER.

SINCE WE'RE TALKING ABOUT THE STRATEGIC PLAN, I WANTED TO JUST GIVE A FEW EXAMPLES. FIRST, I WANT TO MENTION WHAT'S ALREADY BEEN DONE, THE ACCOMPLISHMENTS OF THE CIRM, MANY OF WHICH YOU JUST HEARD ABOUT. FROM THE PERSPECTIVE OF A CONSUMER, I'D LIKE TO SAY THE TRAINING OF THE NEXT GENERATION

OF STEM CELL SCIENTISTS WAS A KEY STEP AND I THINK A VERY INSIGHTFUL ONE TO BEGIN THE PROGRAM. WE NOW HAVE STUDENTS AND POST DOCS AND FELLOWS WHO HAVE BEEN TRAINED IN STEM CELL BIOLOGY, AND MANY OF THEM SPECIFICALLY IN HUMAN EMBRYONIC STEM CELLS. SO THEY'RE PERFECTLY POSITIONED TO TAKE ADVANTAGE OF THE CHANGE IN NIH POLICY NOW.

THE PROMOTION OF HUMAN STEM CELL EXPERIMENTATION SPECIFICALLY HAS TURNED OUT TO BE ACTUALLY A VERY INSIGHTFUL STEP FOR THE CIRM. WE HAVE FACILITIES AND LABORATORIES HERE AT UCSF AND NOW ELSEWHERE ALL OVER CALIFORNIA THAT ARE, AGAIN, VERY WELL POSITIONED TO TAKE ADVANTAGE OF NIH FUNDING NOW FOR NEWLY DEVELOPED CELL LINES. INVESTIGATORS HAVE COME TO CALIFORNIA FROM ALL OVER THE COUNTRY, IN FACT, ALL OVER THE WORLD, WHICH HAS INVIGORATED THE CALIFORNIA POTENTIAL FOR YEARS AND YEARS TO COME. CAREER DEVELOPMENT HAS BEEN SUPPORTED BY THE CIRM, WHICH HAS BEEN CRITICAL FOR RECRUITMENT AS WELL AS FOR DEVELOPMENT OF OUR FACULTY. AND THE CALIFORNIA STEM CELL INDUSTRY HAS BEEN SEEDED HERE, WHICH I THINK IS GOING TO BEAR FRUIT, AS MOST OF US ARE HOPING, IN THE NEXT TEN TO 15 YEARS. AND THEY'VE CREATED A PARADIGM FOR GRANT MANAGEMENT, WHICH I THINK THE NIH IS NOW GOING TO

MODEL WHEN IT COMES TO THEIR STIMULUS PACKAGE IN TRYING TO GET GRANTS OUT THE DOOR IN UNHEARD OF EFFICIENCY.

AND NOW THE EFFORT IS TO DRIVE SOME OF THESE DISCOVERIES TO THE CLINIC. IT'S IN THIS AREA THAT I WANTED TO SPEND THE REST OF MY TIME TALKING ABOUT CLINICAL STEM CELL THERAPIES AND APPLICATIONS. I KNOW THIS AUDIENCE PROBABLY DOESN'T NEED THE REFRESHER, BUT I WANTED TO MENTION THE DIFFERENT WAYS WE NOW HAVE OF MAKING STEM CELLS. THERE'S THE TRADITIONAL HUMAN EMBRYONIC STEM CELL APPROACH FROM THE BLASTOCYST EMBRYO, WHICH HAS NOW BECOME A CLASSIC PARADIGM, ADULT STEM CELLS, OF COURSE, WHICH EXIST AS RESIDENT CELLS IN A VARIETY OF ORGANS IN THE ADULT BODY, AND THEN THE NEW APPROACH OF REPROGRAMMING, USING SKIN CELLS OR OTHER SOMATIC CELLS FROM AN ADULT, A PATIENT, FOR INSTANCE, WITH A DISEASE AND THEN TRANSFORMING THEM INTO A STABLE STEM CELL LINE.

AND NOW WITH THE NIH CHANGE IN POLICY, WE REALLY HAVE THE ABILITY, WHICH I THINK IS NOW UNPRECEDENTED, TO LOOK AT ALL THESE DIFFERENT CELL LINE POTENTIALS AND COMPARE THEM HEAD TO HEAD IN THE SAME NIH-FUNDED LABORATORIES OR LABORATORIES WITH MIXED FUNDING FROM PRIVATE AND FEDERAL SOURCES. SO

I THINK THIS IS A REALLY FABULOUS OPPORTUNITY FOR SCIENTISTS WHO ARE IN THE FIELD OR THOSE WHO WANT TO ENTER THE FIELD NOW.

THE PUSH TO GETTING THERAPIES OUT INTO THE CLINIC, I THINK, HAS SOME RISKS THAT WE SHOULD BE ALL AT LEAST AWARE OF. FIRST IS THE POTENTIAL THAT WE'LL LEARN VERY LITTLE AND AT POTENTIALLY GREAT COST. WHEN I SAY GREAT COST, WHAT I'M CONCERNED WITH IS THE POTENTIAL FOR DOING HARM, THAT THERE MAY BE PATIENTS WHO DEVELOP ADVERSE EVENTS OR TUMORS, AND I THINK THAT IS A REAL RISK.

THE OTHER THING WE HAVE TO KEEP AWARE OF AS AN EXPERIMENT, WHICH, IN FACT, THE DELIVERY OF STEM CELL THERAPIES TO PATIENTS REALLY WILL BE IN THE INITIAL STEPS, WE NEED TO TRY TO LEARN AS MUCH AS WE CAN ABOUT WHAT'S HAPPENING TO THESE CELLS AND WHAT'S HAPPENING TO THE PATIENTS. I THINK WE NEED TO MAKE SURE THERE'S MECHANISMS FOR ACHIEVING SOME OF THESE GOALS, TRACKING THE CELLS. WHERE DO THEY GO? WHAT KINDS OF CELLS DO THEY BECOME? DO THEY EVEN SURVIVE IN THE PATIENTS?

ADVERSE EVENTS WILL BE EASIER, IN FACT, THAN THOSE OTHER QUESTIONS TO DETECT. TUMORS, I THINK, WILL DECLARE THEMSELVES. IMMUNE COMPLICATIONS, HEMORRHAGES, BLEEDING COMPLICATIONS,

INFECTION, ALL THE REST OF THOSE THINGS. I THINK THE ADVERSE EVENTS WE'LL LEARN ABOUT EASILY ENOUGH.

MY CONCERN IS THAT WE MAY NOT LEARN ABOUT THOSE FIRST SET OF QUESTIONS, WHICH ARE REALLY CRITICAL AND CAN'T REALLY BE UNRAVELED IN ANIMAL MODELS.

AND SO LET ME JUST MENTION A FEW SPECIFIC CASES JUST TO SUPPORT SOME OF THESE NOTIONS. MANY OF YOU KNOW THERE'S ALREADY A CLINICAL TRIAL UNDER WAY FOR BATTEN'S DISEASE, AND THIS IS BASED ON THE NOTION THAT THESE STEM CELLS WILL ACT AS DELIVERY VEHICLES FOR A MISSING ENZYME. I BELIEVE SIX PATIENTS HAVE SO FAR BEEN GRAFTED WITH NEURAL STEM CELLS.

I SHOULD MENTION THAT THESE ARE STEM CELLS. THEY AREN'T DIFFERENTIATED INTO NEURONS OR OLIGODENDROCYTES OR ANY OTHER TYPE OF CELL. THEY'RE GIVEN IN THEIR RELATIVELY UNDIFFERENTIATED NEURAL STEM STATE. SO THEY HAVE THE POTENTIAL TO TURN INTO NERVE CELLS OR GLIAL CELL SUPPORT CELLS OR OLIGODENDROCYTES.

SO FAR THERE HAVE BEEN NO ADVERSE EVENTS REPORTED, AS FAR AS WE KNOW NO TUMORS. BUT WE DON'T KNOW FOR SURE THESE PATIENTS HAVE BEEN FOLLOWED LONG ENOUGH. MANY OF YOU ARE PROBABLY AWARE OF THE PAPER

IN *PLOS MEDICINE* MENTIONING THAT THERE WAS A PATIENT TREATED WITH CELLS, NOT TOO UNLIKE THESE NEURAL STEM CELLS, IN RUSSIA AND WHO DEVELOPED AFTER FOUR YEARS MULTIFOCAL TUMORS. HOW LONG WILL IT TAKE TO HAVE TO MONITOR PATIENTS LIKE THIS BEFORE WE KNOW WHETHER THOSE COMPLICATIONS ARE REAL OR NOT IN THIS PARTICULAR CELL TREATMENT?

WHERE DO THE CELLS GO WHEN THEY'RE INJECTED IN THIS CASE INTO THESE CHILDREN? THE PROBLEM IS THAT THE CELLS NEED TO BE DETECTED. AND AS FAR AS I KNOW, THERE ARE NO MARKERS ON THESE CELLS. THEY WEREN'T ABLE TO GENETICALLY MANIPULATE THEM OR TAG THEM IN SOME WAY. SO THE QUESTION IS WILL WE ACTUALLY LEARN WHAT'S HAPPENED TO THE CELLS ONCE THEY'RE DELIVERED? WHAT KINDS OF CELLS HAVE THEY BECOME? DID THEY TURN INTO ASTROCYTES OR OLIGODENDROCYTES OR NERVE CELLS? HOW FAR HAVE THEY MIGRATED? DID THEY WIND UP OTHER ORGANS? HAVE THEY EVEN SURVIVED IN THE PATIENTS? AND, IN FACT, HAVE THEY PRODUCED THE LYSOSOMAL ENZYME REPLACEMENTS THAT EVERYONE HAD HOPED FOR?

SO THESE ARE THE KINDS OF QUESTIONS, I THINK, WE'D LIKE TO LEARN FROM STUDIES LIKE THIS, BUT THEY'RE NOT THE PRIMARY FOCUS OF THE STUDY, AND I'M NOT ENTIRELY SURE YET WHETHER WE'LL ACTUALLY

HAVE ANSWERS TO SOME OF THOSE QUESTIONS.

AND THEN WE HAVE THE SPINAL CORD INJURY TRIAL, WHICH IS NOT STARTED YET, BUT THE FDA HAS GIVEN APPROVAL FOR THAT. AND THIS INVOLVES HUMAN EMBRYONIC STEM CELL-DERIVED OLIGODENDROCYTES, AT LEAST THEORETICALLY THAT'S WHAT THESE CELLS WILL BECOME, AND THEY WILL HOPEFULLY MYELINATE AXONS IN PATIENTS WHO HAD ACUTE SPINAL CORD INJURY. AND THE INITIAL TRIAL IS A PHASE I SAFETY TRIAL OF EIGHT TO TEN PATIENTS WHO WILL BE TREATED JUST WITHIN A WEEK OR TWO OF HAVING THEIR SEVERE SPINAL CORD INJURY.

SO, ONCE AGAIN, SAME SET OF QUESTIONS. WILL WE LEARN ANYTHING ABOUT THESE CELLS? WILL THERE BE A WAY OF TRACKING THE CELLS, OF KNOWING EITHER IN THE LIVING PATIENTS OR LATER ON WHAT'S HAPPENED TO THE CELLS? WHERE HAVE THEY MIGRATED TO? WHERE HAVE THEY GONE? WHAT KINDS OF CELL TYPES HAVE THEY BECOME? HOW MANY OF THEM ARE ACTUALLY OLIGODENDROCYTES? HOW MANY OF THEM HAVE SURVIVED IN THE SPINAL CORD LESION? AND HAVE THEY ACTUALLY MYELINATED THE HOST AXONS AS HOPED? WILL THERE BE SOME WAY OF ACTUALLY ANSWERING ANY OF THOSE QUESTIONS? IT'S UNCLEAR TO ME, AND MAYBE THERE WILL BE, BUT I'M NOT SURE.

AND THEN FINALLY, I THINK A COMPLICATION

HERE IS HOW WILL CLINICAL IMPROVEMENT BE INTERPRETED? IN PATIENTS WHO HAVE SPINAL CORD INJURY ACUTELY IN THE FIRST FEW WEEKS OR SO, THEY EXPERIENCE A GREAT DEAL OF SWELLING, THERE'S INFLAMMATION. THERE ARE A LOT OF CHANGES IN THAT SPINAL CORD THAT WILL ACTUALLY GO AWAY OVER TIME. AND SO MOST PATIENTS WILL SHOW SOME DEGREE OF IMPROVEMENT FOLLOWING THAT ACUTE, SUBACUTE PHASE. IF THESE PATIENTS SHOW THAT EXPECTED DEGREE OF IMPROVEMENT, HOW WILL WE ACTUALLY KNOW WHETHER ANY ADDITIONAL IMPROVEMENT MIGHT HAVE BEEN CAUSED BY THESE CELLS THAT ARE DELIVERED? AND, OF COURSE, THE QUESTION REALLY ISN'T WHETHER THERE IS OR ISN'T IMPROVEMENT. THE QUESTION IS HOW IS THIS GOING TO BE PORTRAYED TO THE PUBLIC? IS THIS GOING TO BE A PHASE I TRIAL THAT SHOWS HOPEFULLY THAT THESE CELLS, IN FACT, SHOW SOME -- THAT THE PATIENTS HAVE SHOWED SOME SIGN OF CLINICAL IMPROVEMENT; THEREFORE, ENCOURAGING THE MOVEMENT TO A PHASE II TRIAL? WILL THERE BE ANY WAY TO KNOW WHETHER THE COURSE OF THESE INITIAL GROUP OF PATIENTS HAS BEEN AFFECTED IN ANY WAY? WILL THAT REQUIRE A LARGER TRIAL? AND THEN, AGAIN, HOW LONG WILL THE PATIENTS HAVE TO BE FOLLOWED BEFORE WE KNOW WHETHER IT'S TRULY SAFE?

SO THERE'S SEVERAL ADDITIONAL NEEDS, I

THINK, FOR STEM CELL TRIALS THAT ARE AREAS WHERE THE CIRM MAY FOCUS SOME ATTENTION. BETTER TOXICITY MODELS ARE NEEDED. LONG-TERM MONITORING, FOR EXAMPLE. RIGHT NOW A YEAR IN AN IMMUNODEPRIVED RAT MAY NOT BE A SUFFICIENT MODEL ESPECIALLY FOR STEM OR PROGENITOR CELL TUMORS WHERE THE TURNOVER RATE MIGHT BE A LOT SLOWER THAN IN HUMAN CELLS, A LOT SLOWER THAN IN ANIMAL CELLS, AND EVEN SLOWER THAN IN HUMAN TUMOR CELLS.

THERE'S A PROBLEM BECAUSE XENOGRAFTS, THAT IS THE ABILITY TO PUT HUMAN CELLS INTO AN ANIMAL MODEL TO LOOK AT TOXICITY, IS A REAL CHALLENGING ISSUE. HUMAN CELLS DON'T SURVIVE WELL IN NONHUMAN PRIMATES, SO YOU CAN'T REALLY LOOK AT LONG-TERM TUMOR FORMATION, FOR INSTANCE, IN A MONKEY WITH A HUMAN CELL GRAFT. PERHAPS A BETTER WAY TO DO THAT MIGHT BE AN ALLOGRAFT; THAT IS, MONKEY STEM CELLS CAN SURVIVE IN MONKEYS, AND MAYBE THAT'S A BETTER MODEL TO LOOK AT FOR A POSSIBLE TOXICITY. THE PROBLEM, OF COURSE, IS THAT THOSE MONKEY CELLS AREN'T GOING TO BE THE HUMAN CELL LINES THAT YOU'D LIKE TO USE FOR THE ACTUAL THERAPIES WE'RE ALL HOPING FOR.

SO IN MANY WAYS I THINK THE TECHNOLOGY HAS A BIT OUTPACED OUR UNDERSTANDING OF WHAT'S GOING ON.

MANY OF THE MAJOR BREAKTHROUGHS THAT WE'RE ALL VERY EXCITED ABOUT IN STEM CELL BIOLOGY HAVE REALLY COME MORE FROM THE BASIC SCIENCE END OF THE SPECTRUM, NEW WAYS OF CREATING STEM CELLS LIKE THE IPS TECHNOLOGY, NEW WAYS OF MAKING THEM SAFER USING THE PIGGYBACK TECHNIQUES, THINGS THAT HAVE JUST BEEN PUBLISHED IN THE LAST FEW WEEKS, THESE ARE VERY EXCITING BREAKTHROUGHS THAT REALLY HAVE THE POTENTIAL TO CHANGE THE WHOLE LANDSCAPE. AND THOSE HAVE REALLY COME OUT OF MORE OF A BASIC SCIENCE END OF THE SPECTRUM, WHICH IS, IN MY VIEW, WHERE I THINK WE STILL NEED TO FOCUS A GREAT DEAL OF OUR EFFORTS. I THINK THAT'S WHERE IN THE LONG TERM WE CAN MAKE THE BIGGEST IMPACT.

I THINK THAT NIH, AS WELL AS THE CIRM, SHOULD INVEST IN THE BASIC BIOLOGY OF BOTH STEM CELLS AND IN THE RELATED AREAS OF DEVELOPMENTAL BIOLOGY THAT REALLY INFORM MANY OF THE STEM CELL STRATEGIES. THAT'S WHAT'S NEEDED TO REALLY BUILD A FOUNDATION OF STEM CELL SCIENCE, WHICH I THINK WILL HAVE THE LONGEST IMPACT WELL BEYOND, SAY, THE TENURE OF THE CIRM. SO I THINK THERE ARE CLEARLY AREAS THAT ARE MATURE ENOUGH TO START THINKING ABOUT CLINICAL APPLICATIONS.

I'D LIKE TO CLOSE JUST BY MENTIONING

ACTUALLY WHAT ALAN ASKED ME TO TALK ABOUT, AN EXAMPLE, FOR INSTANCE, OF A STEM CELL THERAPY THAT MAY MOVE INTO THE CLINIC WITHIN THE FOUR TO FIVE YEARS. AND THAT'S HAPPENING HERE AT UCSF, AND THAT'S PROBABLY THE DIABETES PROGRAM.

WE'VE ORGANIZED, BY THE WAY, OUR STEM CELL PROGRAM ALONG DISEASE-ORIENTED PIPELINES. AND ONE OF THEM, THE ENDOCRINE PIPELINE, IS CO-DIRECTED BY JEFF BLUESTONE IN PARTNERSHIP WITH NOVOCELL, A COMPANY DOWN IN SAN DIEGO. THEY'RE PLANNING A DISEASE TEAM GRANT TO TACKLE DIABETES, ESPECIALLY TYPE 1 DIABETES. AND THE STRATEGY WILL BE TO USE ISLET-LIKE CELLS THAT ARE DERIVED FROM HUMAN EMBRYONIC STEM CELLS AND IMPLANT THEM INTO PATIENTS INITIALLY, OF COURSE, AS A SAFETY TRIAL TO SEE IF THEY CAN REGULATE THEIR INSULIN SECRETION. AND AS A SAFETY FEATURE, THESE CELLS COULD BE EMBEDDED INTO A MATRIX SO THEY COULD BE REMOVED IF THERE'S A PROBLEM IN TERMS OF SAFETY ISSUES. AND SO A PROGRAM IS OBVIOUSLY BEING CONSTRUCTED TO MOVE AHEAD FOR A CLINICAL TRIAL THAT IS, I THINK, FORWARD-LOOKING, THAT IS CAUTIOUS, AND THAT HAS THE POTENTIAL OF ACTUALLY HELPING PATIENTS. AND THERE ARE OTHERS LIKE THIS. IN FACT, THERE ARE MANY MORE THAT I'M PROBABLY NOT EVEN AWARE OF IN CALIFORNIA THAT WILL

EMERGE AS A RESULT OF THE RFA THAT'S ALREADY BEEN ISSUED.

BUT I JUST THINK WE HAVE TO BE CAREFUL THAT, FIRST, THAT WE DON'T RUSH TOO MANY OF THESE TREATMENTS INTO THE CLINIC BEFORE WE REALLY UNDERSTAND EXACTLY WHAT WE'RE DOING. AND, SECONDLY, I THINK WE NEED MORE THAN THAT, TO PLAN THESE EXPERIMENTS CAREFULLY ENOUGH, BECAUSE THEY REALLY ARE EXPERIMENTS, SO THAT WE CAN LEARN FROM THEM. AND WE SHOULD BE PREPARED THAT SOME OF THEM WILL LEAD TO ADVERSE EVENTS ALMOST CERTAINLY, AND THE FIELD NEEDS TO REALIZE THAT THAT'S GOING TO HAVE THE POTENTIAL OF SLOWING THINGS DOWN.

SO I JUST HOPE THAT WHILE WE HAVE THE DISCUSSION NOW FOR THE GOALS OF THE STRATEGIC PLAN FOR THE DURATION OF THE CIRM THAT AT LEAST SOME OF THESE ISSUES ARE KEPT IN MIND. AND MOSTLY AS AN ACADEMIC, I WANT TO MENTION THAT I THINK THE FOUNDATIONS OF STEM CELL BIOLOGY REALLY ARE IMPORTANT AND SHOULDN'T BE OVERLOOKED IN, FOR EXAMPLE, A RUSH TO PUSH THINGS INTO THE CLINIC.

AS A PHYSICIAN I UNDERSTAND WHY IT'S SO IMPORTANT TO DO THIS QUICKLY; THAT IS, TO TRY TO TREAT DISEASES AS SOON AS WE HAVE THE ABILITY TO DO THAT, AND IN SOME AREAS THAT'S FINE. I JUST THINK

WE SHOULD BE A LITTLE BIT CAUTIOUS, AND THAT WOULD BE MY MESSAGE THIS AFTERNOON. THANKS FOR THE OPPORTUNITY, ALAN.

MR. SHEEHY: SO THANK YOU, DR. KRIEGSTEIN. I THINK YOUR WORDS OF CAUTION ARE ALWAYS GOOD TO HEAR. EVEN THOUGH AS A PATIENT ADVOCATE, IT'S NOT THE BEST NEWS, BUT I PERSONALLY HAVE ATTENDED EVERY GRANT REVIEW THAT HAS TAKEN PLACE SINCE THE AGENCY WAS STARTED, AND I'M TREMENDOUSLY IMPRESSED BY THE PROGRESS WE'VE MADE. I KNOW FOR SOME PATIENT ADVOCATES, THEY'D LIKE US TO BE PUTTING STUFF IN PEOPLE RIGHT NOW. AND I THINK TO BE CAUTIOUS AND TO REALLY UNDERSTAND WHAT WE'RE DOING AND TO REALLY LEARN SOMETHING FROM THE EXPERIMENTS THAT WE'RE DOING IS CRITICALLY IMPORTANT.

I ALWAYS THINK THAT THE DEADLIEST THING A REVIEWER CAN SAY IS THAT WHETHER THE EXPERIMENT WORKS OR NOT, WE WON'T BE ABLE TO TELL. WE WON'T REALLY LEARN ANYTHING DEFINITIVELY FROM THIS EXPERIMENT EVEN THOUGH IT'S AN INTERESTING IDEA.

SO WHAT I'D LIKE TO DO NOW IS START TAKING PUBLIC COMMENTS OR QUESTIONS. DR. CSETE IS HERE. ALAN IS HERE. ANY KIND OF INPUT THAT YOU WOULD LIKE TO BE MADE INTO THE STRATEGIC PLAN AS WE MOVE FORWARD IN TRYING DEVELOP THIS INTERIM KIND OF

UPDATE, THAT'S NOT TRULY A NEW STRATEGIC PLAN, BUT JUST AN UPDATE TO KIND OF GET US THROUGH THE NEXT COUPLE OF YEARS.

SO I THINK THERE'S A MIC HERE. MAYBE AMY OR PAT COULD MAYBE TAKE THE MIC AROUND. SO IF SOMEBODY WANTS TO RAISE THEIR HAND.

DR. LUBIN: BURT LUBIN. I'M AT CHILDREN'S HOSPITAL IN OAKLAND. I DIRECT THE RESEARCH PROGRAM. AND WE DO MOSTLY STEM CELL WORK RELATED TO ADULT STEM CELLS FROM THE CORD BLOOD AND NOW FROM PLACENTA AND THE AMNION IN COLLABORATION WITH OUR COLLEAGUES IN VICTORIA.

WHAT I WANTED TO COMMENT ON WAS -- SO I'M A PEDIATRIC HEMATOLOGIST. I WORK AT CHILDREN'S HOSPITAL IN OAKLAND AND DIRECT THE RESEARCH PROGRAM. AND I'M INVOLVED IN CORD BLOOD-RELATED TRANSPLANT RESEARCH AND PLACENTAL CELL RESEARCH. SO I APPRECIATED THE COMMENTS THAT WERE MADE, BUT NOTHING WAS STATED ABOUT HOW WE GOT THE MONEY AND HOW THE PEOPLE IN THE STATE OF CALIFORNIA VOTED FOR CIRM FUNDS RELATED TO A HOPE OF CURE. AND I THINK WHATEVER -- THIS IS NOT TO SAY THAT I DISAGREE WITH THE CAUTION THAT NEEDS TO BE TAKEN, BUT I ALSO THINK THAT IT'S IMPORTANT FOR US TO RECOGNIZE, GIVEN THE POLITICAL CLIMATE AND THE ECONOMIC CLIMATE, WHAT THE

MISSION WAS PROPOSED THAT PEOPLE VOTED FOR IN ORDER TO GET THE FUNDS THAT WE HAVE. I DON'T THINK THERE NEEDS TO BE A DISCUSSION ABOUT THAT, BUT JUST A THOUGHT ABOUT IT.

THE THING THAT I DID WANT TO COMMENT ON IS COMPARING US TO NIH WHERE I'VE BEEN A REVIEWER FOR MANY YEARS, AS DR. KRIEGSTEIN AND OTHERS IN THIS ROOM, PROPOSING CLINICAL TRIALS AND GETTING SUPPORT FOR CLINICAL TRIALS HAS BEEN AN ENORMOUS PROBLEM. AND MOST OF THE FUNDING HAS GONE IN THE NIH TO NONCLINICAL TRIALS BECAUSE THEY'RE EXPENSIVE AND BECAUSE OF A NUMBER OF THINGS THAT WERE POINTED OUT ON THIS SLIDE. SO I THINK THE CHALLENGE OF HOW YOU EMBARK UPON A CLINICAL TRIAL AND HOW YOU DETERMINE EFFICACY, THERE ARE PEOPLE WHO DO JUST CLINICAL TRIAL EVALUATIONS WHO WOULD BE GOOD TO ADVISE CIRM AS TO SOME OF THE ISSUES THAT WERE PRESENTED ON THOSE SLIDES THAT WE MIGHT WANT TO CONSIDER AS WE MOVE FORWARD TO CLINICAL TRIALS BECAUSE THERE ARE WAYS TO ANSWER SOME OF THOSE QUESTIONS. IT JUST REQUIRES MONEY AND A LOT OF MONEY. AND I'M SURE WE'RE GOING TO BE DISCUSSING TODAY WHERE WE STAND ECONOMICALLY GIVEN PRESIDENT OBAMA'S SIGNATURE COUPLE DAYS AGO AND GIVEN THE STATE OF CALIFORNIA'S BUDGET.

SO I JUST THOUGHT THAT IT'S IMPORTANT TO LAY THESE ISSUES OUT. IT'S NOT REALLY A QUESTION. IT'S A CONCERN.

MR. SHEEHY: I DON'T KNOW IF DR. CSETE. I WANT TO ADDRESS PART OF THAT BECAUSE I KNOW THAT WE ARE ACTIVELY IN THE PLANNING STAGE.

DR. CSETE: I THINK I KNOW EVERYBODY IN THE ROOM JUST ABOUT, BUT JUST IN CASE, I'M MARIE CSETE. I'M THE CHIEF SCIENTIFIC OFFICER OF CIRM. AND I THINK BOTH OF YOU HAVE SAID RELATED THINGS.

SO FIRST, SAFETY IS, OF COURSE, OUR FIRST CONSIDERATION HERE. AND, AS YOU KNOW, YOU SAW AN INTERNAL DOCUMENT THAT I WROTE ABOUT THE WIDE RANGE OF SAFETY CONSIDERATIONS THAT WE HAVE TO CONSIDER AS WE GO FORWARD. NO ONE WANTS ANOTHER NAME LIKE JESSE GELSINGER IN THIS FIELD. AND I'M ALSO A PRACTICING PHYSICIAN AND FEEL THE CONTRARY PULLS BETWEEN THE PATIENTS PUSHING US TO GO GO GO FOR SOMETHING THAT THEY HAVE NO GOOD OPTIONS FOR AND THE HEALTH OF THE FIELD IN GENERAL AND THE WAY WE MAKE DECISIONS.

SO I JUST WANT TO ASSURE YOU THAT WE'RE GOING ABOVE AND BEYOND WHAT IS REQUIRED OF US IN TERMS OF THE KINDS OF MONITORING THAT WE WILL HAVE IN PLACE FOR DISEASE TEAMS. AND I THINK IF YOU READ THE DISEASE TEAMS VERY CAREFULLY, THE WAY SAFETY IS

CONSIDERED AS PART OF THAT RUN-UP TO THE CLINIC IS GOING TO BE AN IMPORTANT PART OF HOW THE GRANTS ARE REVIEWED.

SO THE LAST THING THAT -- AND WE ALSO THINK THAT IT'S NOT THE SIGNATURE SO MUCH, BURT, ON THAT PIECE OF PAPER, BUT A SENSE THAT CIRM WILL NOW BE ABLE TO GET ACCESS TO AN ONGOING CONTACT WITH THE PEOPLE AT THE FEDERAL LEVEL WHO ARE INVESTED IN AND EXPERT IN CLINICAL TRIALS. UP UNTIL NOW WE'VE HAD A BIT OF A COLD SHOULDER FROM BOTH THE FDA AND WE HAD NO OFFICIAL MECHANISM FOR WHICH WE COULD BE TALKING TO NIH ABOUT HOW TO SYNERGIZE THESE EFFORTS AND NOT OVERLAP AND MAKE SURE THAT CLINICAL TRIALS HAPPEN IN A REASONABLE TIME WHERE APPROPRIATE.

SO THE CHANGE OF ADMINISTRATION HAS MEANT THAT WE CAN PICK UP THE PHONE AND START GETTING THOSE THINGS IN PLACE. AND WE HAVE SPENT ENORMOUS EFFORT TRYING TO DO THAT. SO ANY OTHER CONTACTS THAT WE DON'T KNOW ABOUT THAT WOULD BE WILLING TO WORK WITH US IN THESE AREAS I'D BE HAPPY TO HEAR ABOUT.

WAS THERE ANOTHER PART OF YOUR --

MR. BROWN: MY NAME IS DAVIS BROWN. IN A SENSE, I GUESS, I REPRESENT THE PARKINSON'S COMMUNITY OF THE NORTH BAY. WE HAVE A NEW

FOUNDATION IN PROGRESS OF DEVELOPMENT FOR PATIENT CARE INITIATIVES. WE ARE CONCERNED IN THE PARKINSON'S COMMUNITY THAT TOO MUCH -- I SHOULDN'T SAY IT THAT WAY. LET ME REPHRASE IT -- THAT A GREAT DEAL OF ATTENTION IS BEING PUT ONTO RESEARCH, BASIC RESEARCH AND APPLIED RESEARCH, AND WE HOPE TOWARD ARRIVING AT A CURE THROUGH STEM CELLS AND/OR OTHER MEANS, BUT IN THE MEANTIME WE'RE ALSO CONCERNED ABOUT THE CARE FOR THE PATIENTS THAT ARE SUFFERING RIGHT NOW.

I HAVE A COLLEAGUE FROM OUR SUPPORT GROUP IN SANTA ROSA WHO IS NOW IN THE HOSPITAL FOR THE LAST WEEK WRITHING IN PAIN AND TRYING TO ADJUST MEDICATIONS AND NOT GETTING TOO FAR WITH IT. AND HE AND OTHERS WOULD WISH FOR THE CHANCE TO PARTICIPATE IN CLINICAL TRIALS. I THINK THAT ONE OF THE PROBLEMS IS THAT CLINICAL TRIALS ARE NOT AS WELL ADVERTISED AS THEY NEED TO BE THROUGH THE PATIENT COMMUNITIES. I DON'T KNOW SPECIFICALLY HOW TO RECOMMEND BETTER WAYS, BUT THERE MUST BE BETTER WAYS BECAUSE WE VERY SELDOM HEAR IN ANY ROUTINE OR ONGOING FASHION ABOUT CLINICAL TRIALS BEING HELD. IT'S SORT OF CATCH AS CATCH CAN, AND I THINK THAT THAT NEEDS TO BE CONSIDERED AS YOU MOVE TOWARD CLINICAL TRIALS.

WE ARE LOOKING FORWARD TO WORKING WITH THE BUCK INSTITUTE, WHICH IS UP OUR WAY, AND OTHERS WHO ARE INVOLVED IN THE STEM CELL RESEARCH PROGRAM, AND WE HAVE GREAT HOPES FOR IT. OUR PARKINSON'S ADVOCATE, JOAN SAMUELSON, I KNOW HAS BEEN VERY ACTIVE ON YOUR BOARD. AND WE ARE AVAILABLE AND WE ARE INTERESTED AND WE'D LIKE TO KNOW WHAT WE CAN CONTRIBUTE TO HELP AND PARTICIPATE IN THE ONGOING PROCESS.

DR. CSETE: I REALLY APPRECIATE THOSE COMMENTS. SO, FIRST, I HOPE, IF YOU ARE NOT AWARE OF WHAT SOUNDS LIKE A VERY SIMILAR GROUP THAT'S FORMED FOR PATIENT CARE ISSUES AROUND PARKINSON'S IN SOUTHERN CALIFORNIA. I CAN PUT YOU IN TOUCH WITH THAT GROUP. I THINK THEY'VE DONE SOME VERY WORTHWHILE THINGS. JIM HUANG, WHO I MET AT A BOARD MEETING IS THE PERSON WHO, AS A PATIENT ADVOCATE, STARTED THAT GROUP. AND I THINK IT'S REALLY IMPORTANT FOR US TO KEEP CONTACT WITH THE PATIENT ADVOCATES AT CIRM, AND I WOULD WELCOME YOU TO COME IN AND JUST SIT WITH ME FOR A BIT BECAUSE I THINK IT'S GREAT. WE CAN'T DO PATIENT CARE. THAT'S NOT -- WE'RE NOT A HOSPITAL, AND IT'S NOT WHAT WE DO, BUT I THINK IT'S REALLY IMPORTANT FOR OUR PATIENT CARE -- PEOPLE INTERESTED IN PATIENT CARE

AND PATIENT ADVOCATES TO BE INVESTED IN THE RESEARCH COMMUNITY AND HAVE AN ONGOING JUST OPEN COMMUNICATION WITH IT. WE'VE BEEN VERY SUCCESSFUL IN DOING THAT WITH OTHER DISEASES.

IN TERMS OF CLINICAL TRIALS, THE ONES THAT REACH REGISTRATION AT THE NATIONAL LEVEL AND ARE APPROVED BY THE FDA ARE ALL EASILY ACCESSIBLE BY PERIODICALLY CHECKING ON CLINICALTRIALS.GOV. WHEN YOU GO TO THAT WEBSITE, YOU CAN TYPE IN THE DISEASE OF INTEREST AND THE CITY, AND YOU WILL THEN GET A READING OF ANYTHING THAT'S REGISTERED WHERE PATIENTS FROM YOUR GEOGRAPHIC AREA ARE ELIGIBLE, AND THE SITE WILL ALSO TELL YOU IF THEY'RE ENROLLING, IF ENROLLMENT IS CLOSED, WHAT THE SPECIFIC KINDS OF PATIENTS ARE THAT ARE ELIGIBLE.

WE GET REQUESTS ALL THE TIME ABOUT HEARING ABOUT CLINICAL TRIALS FROM VARIOUS PATIENT GROUPS, AND WE DO HEAR ABOUT SOME CREDIBLE ONES IN EUROPE. WE'RE HAPPY TO SHARE THAT INFORMATION WHEN WE HAVE IT, BUT WE ALWAYS REFER PEOPLE BACK TO THE CLINICAL TRIALS WEBSITE.

MR. BROWN: IF I COULD COMMENT ON THAT, I THINK THAT ONE OF THE PROBLEMS IS, AS WAS POINTED OUT HERE BY ONE OF THE PRESENTERS, TECHNOLOGY IS GETTING AHEAD OF UNDERSTANDING. AND THE TECHNOLOGY

OF THE WEB AND THE INFORMATION CAPABILITIES THAT IT HAS FOR PROVIDING ARE NOT AS WELL ABSORBED BY THE OLDER GENERATION THAT'S SUFFERING FROM THE DISEASES AS THE YOUNGER GENERATION WOULD LIKE TO EXPECT THAT THEY ARE. AND, THEREFORE, THEY DON'T JUMP TO THE COMPUTER EVERY HOUR ON THE HOUR TO CHECK THEIR E-MAIL AND SO FORTH AND SO ON, AND THAT INCLUDES ME. ALTHOUGH I UNDERSTAND THE TECHNOLOGY AND I USE IT WHEN I CAN, I'M NOT A COMPUTER FREAK AND I DON'T GET INVOLVED IN THESE THINGS. BUT WE NEED SOMEBODY WHO DOES, BUT WE NEED TRAINING FOR THOSE PEOPLE TOO.

DR. CSETE: I THINK IT'S ALSO INCUMBENT ON YOU TO JUST REMIND YOUR PHYSICIANS PERIODICALLY TO CHECK THAT WEBSITE IF THEY'RE NOT GETTING REGULAR UPDATES.

MR. BROWN: BUT THE QUESTION IS, YOU KNOW, IS THAT REALLY THE END ALL OF IT, OR SHOULD WE BE LOOKING AT ANOTHER PROCESS THAT INCORPORATES THAT, THAT TRAINS PEOPLE TO BE THE INFORMATION FLOW PEOPLE, IF YOU WILL, AND THAT GET -- THAT ACT AS AN INTERMEDIARY TO HELP DISPERSE THIS INFORMATION OUT TO THE BROADER AUDIENCE OF PATIENTS THAT ARE EITHER INCAPABLE OR NOT AVAILABLE OR DON'T HAVE THE FACILITIES AVAILABLE TO GET INTO THE WEBSITES AND DO THEIR OWN RESEARCH AT A LOCAL LEVEL. I THINK THAT'S

A REALLY IMPORTANT POINT THAT NEEDS TO BE CONSIDERED AS WE WHO ARE SMARTER ABOUT THESE THINGS, IF YOU WILL, RACE THROUGH THE PROCESS. I THINK YOU'RE MISSING SOME OF THE PEOPLE THAT YOU ARE TRYING TO HELP. DOES THAT MAKE SENSE?

DR. CSETE: YEAH. WE HAVE A COMMUNICATIONS OFFICE. AND, AGAIN, WE DON'T HAVE A PROCESS TO PICK UP THE PHONE AND CALL PEOPLE, BUT WE DO HAVE PRESS RELEASES AND WE DO HAVE BLAST E-MAILS -- AGAIN, IT'S TECHNOLOGY -- E-MAIL MAILINGS TO ANYONE WHO'S INTERESTED IN HEARING OF UPDATES. I'M QUITE CERTAIN THAT WE WOULD MAKE LOCAL ANNOUNCEMENTS IF WE WERE FORTUNATE ENOUGH TO REACH A CLINICAL TRIAL THAT WAS FUNDED BY CIRM.

I THINK THIS IS SOMETHING THAT OUR CLEVER COMMUNICATIONS PEOPLE CAN CHEW ON, AND IT'S A VERY GOOD SUGGESTION.

MR. BROWN: IF I MAY, IN PASSING THE MIC BACK, I WOULD LIKE TO JUST SAY THAT SINCE THE VERY EARLY START-UP OF CIRM WHEN I ATTENDED SOME OF YOUR MEETINGS OVER IN SACRAMENTO, I'D LIKE TO COMPLIMENT YOU ON THE PROGRESS YOU'VE MADE IN SPITE OF GREAT ODDS FROM THE WASHINGTON, D.C. LEVEL. I'M GOING BACK TO D.C. FOR THE PARKINSON'S ACTION NETWORK FORUM NEXT WEEK, AND I LOOK FORWARD TO SEEING HOW

THE SYSTEM IS CHANGING BACK THERE. AND I JUST WANT TO THANK YOU VERY, VERY MUCH FOR ALL THAT YOU ALL ARE DOING HERE. I THINK YOU'VE GOTTEN A GREAT LEAD OVER SOME OTHER PARTS OF THE COUNTRY, AND WE JUST HOPE THAT YOU'LL CONTINUE THAT ALONG AND INCORPORATE US INTO YOUR THINKING IN ANY WAY POSSIBLE.

MR. SHEEHY: IF I CAN JUST ADD SOMETHING, I THINK BRUCE HAS HIS HAND UP. JOAN, I THINK ONE OF THE BEST THINGS ABOUT THIS EXPERIENCE BEING ON THE BOARD IS GETTING TO BE FRIENDS WITH PEOPLE LIKE JOAN. US ADVOCATES TEND TO BE IN OUR SILOS. WE ALL HAVE OUR PARTICULAR DISEASES. AND BEING ABLE TO HAVE A BROADER SENSE OF WHAT OTHER CHALLENGES ARE FOR OTHER PEOPLE WHO HAVE OTHER DISEASES HAS BEEN REALLY AN AMAZING EXPERIENCE. SO JOAN HAS BECOME A DEAR FRIEND OF MINE.

I WOULD LIKE TO SAY WE HAVE BEEN DISCUSSING, AT LEAST SOME OF BOARD MEMBERS, EXACTLY WHAT YOU'RE TALKING ABOUT. AND THE REASON IS BECAUSE IF WE CAN GET ROBUST PARTICIPATION BY THE ADVOCACY GROUPS, BY PATIENTS, AS WE START TO GO INTO CLINICAL TRIALS, WE CAN START TO CHANGE THE RISK-REWARD RATIO AT THE FDA. WE'VE SEEN THIS IN HIV. MY DEAR FRIEND JEFF GETTY, WHO GOT THE BABOON MARROW TRANSPLANT, WHY WOULD YOU LET ANYBODY DO

THAT? WELL, HIS FAMILY CAME AND CRIED AT THE FDA HEARING. THEY'RE NOT WORRIED ABOUT GETTING SUED OR PEOPLE GETTING REALLY ANGRY WHEN THE FAMILY IS BEGGING YOU TO DO THIS EXPERIMENT.

AND INTERESTING ENOUGH, SOME OF THE BOARD MEMBERS WHO HAVE BEEN REALLY ENGAGED IN TRYING TO CARRY ON THESE DISCUSSIONS HAVE BEEN SOME FOLKS FROM INDUSTRY BECAUSE THEY RECOGNIZE TOO, AS THE PEOPLE WHO ARE GOING TO BE TAKING SOME OF THESE THINGS INTO CLINICAL TRIALS, THAT IF YOU HAVE THIS TIGHT RELATIONSHIP WITH THE ADVOCACY COMMUNITY, IT WILL BE EASIER TO GO FORWARD. YOU'LL GET -- EASY TO RECRUIT PATIENTS, THE WHOLE THING CAN KIND OF WORK BETTER.

SO I THINK PART OF IT IS WE'RE NOT -- WE'RE STILL FEELING AS AN AGENCY HOW WE'RE GOING TO WORK INTO THE CLINICAL TRIAL FIELD. I THINK AS WE'VE HEARD FROM DR. KRIEGSTEIN, THE FIELD IS NOT -- WE'RE STILL KIND OF TENTATIVELY HEADED THAT DIRECTION, BUT WHAT YOU ARE TALKING ABOUT IN TERMS OF HAVING THE ADVOCACY COMMUNITY INTIMATELY INVOLVED IN THIS, WELL-INFORMED, AVAILABLE TO PARTICIPATE, I THINK THAT FOR THE PATIENT ADVOCATE BOARD MEMBERS OF THE CIRM, WE'RE ACTIVELY THINKING ABOUT THAT, AND WE REALLY WANT TO SEE THAT HAPPEN.

DR. CONKLIN: FIRST, I JUST WANTED TO

ACTUALLY ADD THAT IT'S ACTUALLY INSPIRATIONAL TO HAVE THE PATIENT GROUPS INVOLVED. I THINK THAT THAT'S SOMETHING THAT'S VERY DIFFERENT THAN THE NIH IN THE SENSE THAT WE'RE NOT ATTACHED TO THE PATIENT GROUPS VIA NIH THE WAY WE ARE WITH CIRM. I THINK THAT THAT'S REALLY BEEN INSPIRATIONAL.

THE SECOND THING, JUST COMPARING CIRM TO NIH, IT'S REALLY THE TRANSPARENCY OF THE REVIEW PROCESS IS REALLY ADMIRABLE, I THINK, AND SOMETHING WHICH A LOT OF PEOPLE DIDN'T THINK WOULD WORK. BUT BEING ABLE TO HAVE YOUR OWN -- REVIEWS OF YOUR GRANTS POSTED ON THE INTERNET WAS INITIALLY A SCARY PROCESS, BUT HAS ACTUALLY TURNED OUT TO BE A REALLY POSITIVE EXPERIENCE IN THE SENSE THAT YOU ACTUALLY END UP CREATING COLLABORATIONS AND THINGS LIKE THAT BY READING OTHER PEOPLE'S REVIEWS AND SAYING YOU'RE DOING THIS TOGETHER. WE SHOULD WORK TOGETHER, ETC.

THE POINT -- THE QUESTION THAT I HAD, THOUGH, AFTER THOSE TWO COMMENTS IS THAT INITIALLY THERE WAS A REALLY LASER-LIKE FOCUS ON EMBRYONIC STEM CELLS, SOMETHING FROM EMBRYONIC STEM TISSUE. THEN THERE WAS THE IPS REALLY WONDROUS DISCOVERY THAT I THINK -- AND VERY WISELY, I THINK CIRM OPENED THE DOOR A BIT TO WORKING WITH IPS CELLS. AND I THINK THAT THAT'S BEEN -- I THINK IT'S A WISE THING

BECAUSE FUNCTIONALLY THEY'RE PLURIPOTENT AND SO ON.

THE QUESTION I HAVE IS JUST IS IT OPENING AGAIN TO NOW A BROADER THING FOR MESENCHYMAL STEM CELLS, OR IS IT GOING TO STAY FOCUSED ON SOMETHING THAT STARTS WITH PLURIPOTENT STEM CELLS BECAUSE IT DOES AFFECT HOW WE PUT TOGETHER GRANTS AND THINGS LIKE THAT? AND IT'S NOT A HUNDRED PERCENT CLEAR AT LEAST TO ME.

DR. CSETE: WE'RE DEFINITELY OPENING FOCUS. SO THERE'S, AGAIN, A BALANCE HERE. FIRST AND FOREMOST, WE WANT TO GET TO THE END GAME, WHICH IS CURES. WHATEVER TOOL GETS YOU THERE BEST, AS LONG AS IT'S BASED SOMEHOW IN STEM CELL BIOLOGY, I THINK IS WELL WITHIN THE FRAME OF OUR MISSION. AND YOU WILL NOTICE THAT I THINK WE'VE REALLY EMBRACED IPS, NOT SO MUCH THINKING THAT THAT'S GOING TO BE THE FIRST CELL INTO A PLURIPOTENT CELL THERAPY, BUT BECAUSE THE POTENTIAL FOR REALLY BEAUTIFUL DISEASE MODELS IN A DISH THAT CAN BE USED FOR HIGH THROUGHPUT SCREENING AND DEVELOPMENT OF DRUG THERAPIES, THAT'S ALL PART OF DISEASE TEAMS AND CERTAINLY IT'S OUR VISION FOR THIS PIPELINE. SO THAT REALLY OPENED THE SPECTRUM OF HOW STEM CELL BIOLOGY COULD HAVE A REACH INTO DISEASES WHERE WE REALLY DIDN'T HAVE A REACH BEFORE.

AND AS YOU WELL KNOW, WE ALSO FELT VERY STRONGLY THAT FOR NEW FACULTY, WHICH WAS A VERY LARGE INVESTMENT IN THE FUTURE OF CALIFORNIA SCIENCE, WE DIDN'T WANT THEM TO NECESSARILY HAVE TO WAIT. WE WANTED THEIR GOOD DEVELOPMENTAL BIOLOGY AND ADULT STEM CELL WORK TO BE RIGHT OFF THE GROUND SO THAT THEY COULD MAKE HEADWAY. AND A GOOD PERCENTAGE OF THE NEW FACULTY AWARDS ARE FOR ADULT STEM CELL WORK THAT WE THINK ARE WORKING THEIR WAY TOWARDS THE CLINIC. SO ABSOLUTELY WE'VE OPENED THE DOOR.

ONE OF THE THINGS, I THINK, THAT WE HAVE TO BE REALLY CONSCIOUS OF WAS THE SENSE THAT WHEN CALIFORNIA VOTED FOR CIRM, THEY VOTED FOR IT AS A CALIFORNIA SPECIAL THING. AND SO AS PART OF OUR REVIEW PROCESSES, WE CONTINUE TO HAVE A METRIC FOR THE REVIEWERS, ONE OF THE CRITERIA BEING COULD THIS BE FUNDED BY OTHER MECHANISMS? NOW, WHAT'S HAPPENING AT NIH SUGGESTS THAT SOME OF THE BASIC SCIENCE COULD WELL BE FUNDED BY OTHER MECHANISMS; BUT JUST BECAUSE OF THE SCALE OF SOME OF THE GRANTS THAT WE'RE NOW PROPOSING AND A LITTLE BIT BECAUSE SOME OF THEM ARE STILL MORE IDEA-BASED THAN PRELIMINARY DATABASED, WE WILL STILL HAVE A BODY OF GRANTS THAT -- APPLICATIONS THAT BECAUSE OF THE

NATURE OF THE RESEARCH OR THE SCALE OF THE RESEARCH COULD NOT BE FUNDED BY ANY OTHER MECHANISM, PARTICULARLY WHEN WE HAVE ALL THESE PARTNERS NOW INVOLVED.

SO THAT'S THE TENSION THAT WE HAVE TO WORK WITH, BUT WE CERTAINLY HAVE OPENED UP THE DOORS TO THE BEST POSSIBLE STEM CELL-BASED RESEARCH THAT CAN LEAD TO CURES.

MR. SHEEHY: COULD I ASK DR. CONKLIN WHAT HIS FEELING IS BECAUSE I THINK THIS IS AN INTERESTING KIND OF QUESTION IF PEOPLE HAVE THOUGHTS. BECAUSE I KNOW FROM SITTING IN THE REVIEWS, THERE WAS A POSITIVE BIAS AGAINST ANYTHING THAT WASN'T ES CELLS. WHY NOT? WE WERE THE ONLY PEOPLE WHO COULD DO THIS. WE HAD REVIEWERS COMING FROM AROUND THE COUNTRY, AND THEY WERE REALLY ENERGIZED BY THE TYPES OF EXPERIMENTS THAT PEOPLE IN THIS ROOM WERE DOING AND WANTED TO SEE THAT GO FORWARD, AND ADULT STEM CELLS OR SOMETHING THAT MIGHT GO TO THE NIH WAS JUST NOT THAT FUN.

BUT NOW THAT THE NIH CAN FUND A LOT OF THIS, WHAT SHOULD WE DO? I THINK THIS IS A REALLY INTERESTING QUESTION FOR US. SHOULD WE -- IF YOU'RE LOOKING DOWN THE DEVELOPMENTAL PIPELINE, IF WE DO MORE ADULT STUFF, WE CAN DO MORE STUFF CLOSER TO THE

CLINIC.

DR. CONKLIN: JUST I HAVE TWO COMMENTS ON THAT, I THINK. ONE IS THAT IT'S VERY DIFFICULT TO -- IT'S RELATIVELY EASY TO DEFINE WHAT A PLURIPOTENT STEM CELL IS. WHAT AN ADULT STEM CELL IS IS DIFFICULT TO DEFINE. SO WHEN YOU -- ONCE YOU OPEN THE DOOR TO THAT, IT'S VERY BROAD IN TERMS OF WHAT IT IS. AND SO THERE WILL BE A DILUTIONAL EFFECT. THE ADVANTAGES, OF COURSE, THAT YOU CAN -- YOU HAVE A MUCH BIGGER PLAYING FIELD. THE DISADVANTAGE IS THAT THE ADULT STEM CELLS ARE REALLY NOW COMMITTED TO A SPECIFIC DISEASE; WHEREAS, DISCOVERIES MADE IN PLURIPOTENT STEM CELLS HAVE A CROSSOVER SECONDARY GAIN.

FOR INSTANCE, MY WORK IS PRIMARILY ON CARDIAC; BUT BECAUSE WE'RE WORKING ON PLURIPOTENT STEM CELLS AND WE'RE FOCUSING ON THAT, WE MAY HAVE A DISCOVERY WHERE, FOR INSTANCE, OUR FAILED EXPERIMENT IS THAT ALL WE MAKE IS DOPAMINURGIC NEURONS, AND THAT COULD BE SEEN AS A SUCCESS FOR MY PATIENT ADVOCATE IN FRONT OF ME HERE; WHEREAS, THAT'S UNLIKELY TO HAPPEN WORKING WITH, SAY, SKIN CELLS THAT ARE ESSENTIALLY COMMITTED IN THE SKIN CELL LINEAGE ESSENTIALLY. SO THERE'S A DILUTIONAL EFFECT, BUT THERE'S OBVIOUSLY ADVANTAGES. SO I SEE

ADVANTAGES ON BOTH SIDES.

WHAT I DEFINITELY SEE, THOUGH, AS A MEMBER OF A DISEASE TEAM, FOR INSTANCE, IS AS WE MOVE FORWARD, HOW WE MAKE OUR PLANS MAY BE DIFFERENT IN TERMS OF WHAT WE PLACE IN, FOR INSTANCE, IN A DISEASE TEAM. WE'RE ACTIVELY DOING THAT CARDIAC, FOR INSTANCE, AND I THINK THAT THERE ARE OTHER GROUPS AS WELL MAKING SIMILAR SORTS OF DECISIONS. AND I THINK THAT IT'S IMPORTANT FOR US TO KNOW WHAT THE PLAYING FIELD IS ESSENTIALLY. AND TO BE HONEST WITH YOU, WHAT CELESTE JUST SAID WAS NEWS TO ME. I'M SORRY. MARIE.

DR. CSETE: I WOULD ENCOURAGE YOU TO READ THE RFA'S VERY CAREFULLY BECAUSE WE DO SET THOSE PARAMETERS IN EACH ROUND. AND THOSE THINGS, THOSE PARAMETERS, COULD CHANGE WITH EACH ISSUING OF THESE CORE GRANTS. BUT RIGHT NOW FOR DISEASE TEAMS, THERE WILL BE GROUPS WORKING WITH PLURIPOTENT HUMAN EMBRYONIC STEM CELL-DERIVED CELL THERAPIES. WE ANTICIPATE NOVEL APPLICATIONS OF ADULT STEM CELLS. WE ANTICIPATE DRUG AND BIOLOGIC DEVELOPMENT AS PART OF IT, AND WE'RE LOOKING FOR THE BEST, MOST READY SCIENCE FOR WHICH THERE'S A HUGE UNMET MEDICAL NEED. SO I THINK WE'VE SET OUT THOSE CRITERIA. YEAH, IT'S BROAD. IT'S MUCH MORE OF A CHALLENGE FOR US BECAUSE

WE'LL BE COMPARING APPLES TO ORANGES.

BUT KEEPING THE EYE ON THE HORIZON, READINESS FOR A NEW THERAPY THAT REALLY FUNDAMENTALLY CHANGES THE WAY PATIENTS WITH A CERTAIN DISEASE CAN BE TREATED IS STILL FOREMOST IN OUR MIND. SO WHATEVER TOOL YOU USE, THAT'S OKAY WITH US. BUT WE'RE REALLY COUNTING ON THE SCIENTISTS TO GET US THERE.

DR. GREEN: MY NAME IS WARNER GREEN FROM THE GLADSTONE INSTITUTE. I WANTED TO GO BACK TO THIS ISSUE OF THE INTERPLAY NOW BETWEEN CIRM AND NIH SINCE NIH IS OPENING UP STEM CELL RESEARCH. I'D JUST LIKE TO MAKE THE POINT THAT I CERTAINLY HOPE THAT CIRM DOES NOT TURN OVER THE REINS OF BASIC SCIENCE TO THE NIH BECAUSE I'M NOT CERTAIN THAT WE CAN COUNT ON THE NIH IN TERMS OF PAYLINES AFTER THE STIMULUS PACKAGE. NO ONE KNOWS WHAT'S GOING TO HAPPEN.

AND I ALSO THINK THAT IT'S FOOLISH TO THINK THAT WE HAVE THE KNOWLEDGE NOW FOR THE DISEASE TEAMS TO SUCCEED. INDEED, I SUSPECT THAT YEARS OF BASIC SCIENCE ARE NEEDED TO REALLY SOLIDLY POSITION THE DISEASE TEAMS TO SUCCEED IN THE TASKS THAT THEY ARE ATTEMPTING. SO I THINK THAT WHILE THERE IS THIS -- I'M SURE THERE'S THIS URGENCY TO DELIVER

TO THE STATE OF CALIFORNIA, TO THE POPULATION THE MIRACLE STEM CELL THERAPY, I WOULD SUGGEST THAT WE'RE IN THIS FOR THE LONG RUN. THE TECHNOLOGY IS TREMENDOUSLY EXCITING, BUT WE CANNOT EITHER DELEGATE TO OTHERS OR FORFEIT THE INVESTMENT IN THE BASIC SCIENCE NEEDED TO ENSURE THE LONG-TERM SUCCESS OF THIS INITIATIVE.

DR. CSETE: WE DO THIS AT EVERY MEETING. IT SEEMS WE'RE REASSURING YOU THAT BASIC BIOLOGY, WE'RE NOT ABANDONING BASIC BIOLOGY. IT'S A PART OF THE CORE GRANTS. AND THE CORE GRANTS WERE DESIGNED TO COVER THE FULL PIPELINE.

WE DON'T KNOW WHAT OUR RELATIONSHIP WITH NIH IS GOING TO BE BECAUSE WE HAVEN'T REALLY ESTABLISHED IT YET. WE'RE JUST LOOKING FORWARD TO IT. BUT THE IDEA HERE WOULD BE THAT WE DO HAVE A SHORTER TERM HORIZON BECAUSE OF THE MANDATE OF THE WAY THE PROPOSITION IS WRITTEN. SO WE WILL BE LOOKING FOR THINGS THAT ARE READIER FOR CLINICAL THAN NOT, AND THE NIH TENDS TO FUND RESEARCH THAT HAS A LONGER TIME HORIZON. SO WE WANT TO MAKE SURE THAT OUR EFFORTS ARE SYNERGISTIC RATHER THAN OVERLAPPING, BUT THE MOST IMPORTANT THING IS THAT WE HOPE TO CAPITALIZE ON THE KIND OF BASIC RESEARCH RESULTS THAT ARE COMING BACK TO US.

I MEAN I HAD GREAT PLEASURE READING YOUR PROGRESS REPORT. IT WAS ONE OF THE MOST BEAUTIFUL THINGS I'D SEEN. THOSE ARE THE KINDS OF THINGS THAT WE'VE STARTED THAT WE REALLY HOPE TO CONTINUE WITH.

MR. SHEEHY: I DON'T THINK WE ACTUALLY PRESENTED WHAT THE CORE GRANTS WERE. IT MIGHT BE HELPFUL, AND THESE WILL REPEAT ROUGHLY ON AN ANNUAL 12- TO 18-MONTH BASIS.

DR. CSETE: SO THE IDEA WITH THE CORE GRANTS WAS THAT BASIC BIOLOGY WOULD COVER THE DISCOVERY SCIENCE, THAT EARLY TRANSLATION WOULD WORK ON BOTTLENECKS TO TRANSLATION AS WELL AS DEVELOPMENT OF POTENTIAL CANDIDATES FOR THERAPIES, AND THEN THE DISEASE TEAMS WOULD GO FROM THE EARLY TRANSLATION MODE, MAKE A DECISION ABOUT WHETHER A CANDIDATE WAS READY FOR PRECLINICAL DEVELOPMENT AND THE INVESTMENT IN WORKING TOWARDS AN IND. SO BASICALLY THOSE THREE CORE GRANTS, BASIC BIOLOGY, EARLY TRANSLATION, AND DISEASE TEAMS, COVER THAT VALLEY OF DEATH THAT WE TALKED ABOUT -- THAT ALAN TALKED ABOUT.

AND SO THAT CALCULATION WAS MADE SO THAT WE ARE DOING THE KINDS OF SCIENCE NECESSARY TO MEET OUR MISSION, BUT ALSO TO MAKE THE CYCLIC APPEARANCE OF THE GRANTS SOMETHING THAT WAS MUCH MORE UNPREDICTABLE FOR THE SCIENTISTS UP UNTIL NOW. SO

WE'LL GET ON A MORE REGULAR SCHEDULE SO YOU KNOW WHEN THINGS ARE COMING OUT.

DR. BERNSTEIN: MY NAME IS HAROLD BERNSTEIN. I'M A PEDIATRIC CARDIOLOGIST AT UCSF CHILDREN'S HOSPITAL AND A CELL BIOLOGIST. SO I WANTED TO MAKE THREE COMMENTS.

FIRST, I WANT TO ECHO WHAT DR. GREEN AND DR. KRIEGSTEIN SAID IN THAT I THINK AS A SCIENTIFIC COMMUNITY, WE'RE REALLY ETHICALLY OBLIGATED TO HELP EXPLAIN TO THE PATIENT ADVOCACY COMMUNITY WHY CLINICAL TRIALS WOULD BE PREMATURE IN CERTAIN INSTANCES AND WHEN CLINICAL TRIALS WOULD BE APPROPRIATE, ESPECIALLY FOR THOSE OF US WHO TAKE CARE OF PATIENTS AND REALIZE THAT IT WOULD BE GREAT TO HAVE A THERAPY THAT WOULD SAVE THIS PATIENT'S LIFE AND THAT WITHOUT THAT, A PATIENT THAT WE TAKE CARE OF AND CARE ABOUT MAY NOT SURVIVE. BUT DESPITE THAT, WE NEED TO BE RESPONSIBLE. AND WE NEED TO BE RESPONSIBLE TO THE PEOPLE OF CALIFORNIA.

SECONDLY, I WANT TO ECHO WHAT BRUCE CONKLIN SAID ABOUT THE MERITS OF WORKING WITH PLURIPOTENT STEM CELLS AS OPPOSED TO TISSUE-SPECIFIC OR ADULT STEM CELLS. AND I HAD TO SMILE AT BRUCE'S COMMENT BECAUSE THROUGH CIRM-FUNDED RESEARCH, ALTHOUGH MY LAB SPECIFICALLY IS TRYING TO LOOK AT

WAYS TO MAKE STEM CELLS THAT WILL IMPROVE HEART DISEASE, WE STUMBLED ONTO A SUBSET OF STEM CELLS THAT TURNS OUT TO MAKE NEURAL PRECURSOR CELLS. AND WITHOUT HAVING DONE -- APPROACHED THIS FROM THE PERSPECTIVE OF LOOKING AT PLURIPOTENT STEM CELLS, WE NEVER WOULD HAVE MADE THAT DISCOVERY, WHICH HOPEFULLY OTHER GROUPS WILL BE ABLE TO CAPITALIZE ON.

AND FINALLY, I WANT TO MAKE A SECOND COMMENT ON THE ISSUE OF THE FOCUS ON USING PLURIPOTENT EITHER EMBRYONIC OR INDUCED PLURIPOTENT STEM CELLS, THAT IT'S REALLY HEARTENING TO SEE THAT THERE'S BEEN A CHANGE AT THE FEDERAL LEVEL, BUT NIH NOW HAS A LOT OF WORK TO DO TO DETERMINE HOW THEY'RE GOING TO GO ABOUT FUNDING EMBRYONIC STEM CELL WORK. AND IT IS GOING TO TAKE SOME TIME. IN ADDITION, AS DR. GREEN POINTED OUT, THERE REALLY HASN'T BEEN ANY INCREASE IN THE BASE OF THE NIH BUDGET. AND GIVEN THE ECONOMY, IT'S UNLIKELY THAT'S GOING TO HAPPEN IN THE NEAR FUTURE. SO I DON'T THINK WE CAN RELY ON NIH.

IN ADDITION, CIRM HAS ALREADY MADE A CONSIDERABLE INVESTMENT IN FUNDING A TYPE OF RESEARCH THAT REALLY IS NOT GOING ON IN MANY PLACES AROUND THIS COUNTRY. AND WE'RE NOW POSED REALLY TO

TAKE ADVANTAGE OF THIS INVESTMENT, TO REALLY GET THE REWARD FROM IT.

AND I THINK WHILE I AGREE WITH THE COMMENTS THAT WERE MADE, THAT ANYTHING THAT LOOKS TO BE A PROMISING THERAPY SHOULD BE EXPLORED FULL BORE BECAUSE WHAT WE REALLY WANT IS TO HELP OUR PATIENTS, THAT WE HAVE MADE THIS INVESTMENT. WE'RE REALLY ABOUT TO SEE A RETURN ON IT, AND WE SHOULDN'T LOSE SIGHT OF THAT.

DR. CSETE: WE'RE ALL TALKING THE SAME LANGUAGE. FOLLOWING UP ON THIS $600 MILLION INVESTMENT, AND REALLY ALMOST THE VAST MAJORITY PLURIPOTENT STEM CELL WORK, IS EXACTLY WHAT'S STARTING TO HAPPEN NOW. THE BEST OF THESE ARE THINGS THAT WE HOPE THESE MECHANISMS WILL ALLOW PEOPLE TO CONTINUE WITH. SO WE TIMED THE APPEARANCE OF BASIC BIOLOGY PERFECTLY TO CAPTURE ON THIS FIRST ROUND THE SEED GRANTS THAT WERE DOING WELL AND FINISHING UP ON TIME AND IN THE NEXT ROUND FOR THE SEED GRANTS THAT WERE DELAYED BECAUSE OF ADMINISTRATIVE AND OTHER ISSUES.

SO THE WHOLE IDEA IS TO MAKE SURE THAT OUR INVESTMENT GETS CARRIED FORWARD TO THE NEXT LEVEL. ABSOLUTELY.

DR. LOMAX: THANK YOU. GEOFF LOMAX FROM

CIRM. I JUST WANTED TO CONVEY A COMMENT RECEIVED VIA E-MAIL FROM THE NATIONAL ASSOCIATION OF HEPATITIS TASK FORCES. SO IF I JUST MAY READ THROUGH THIS, THAT WAS THE REQUEST. AND THE COMMENT IS FROM -- THE REQUEST IS FROM BILL REMAK.

"OUR BOARD OF DIRECTORS AND MEDICAL ADVISORS WISHES TO CONVEY THEIR SUPPORT FOR A MOVEMENT AND DIRECTION THAT WILL PROCEED WITH A FAIR-MINDED APPROACH TO ADVANCED RESEARCH IN THE AREA OF LIVER DISEASE. HOWEVER, WE DO ACKNOWLEDGE THAT FOR THE PURPOSE OF EXPEDIENCY AND SAVING LIVES, THAT A FOCUS MAY LEAN IN THE DIRECTION OF WHERE THE RESULTS MAY BE MORE OPPORTUNISTIC.

"WE WISH TO CONVEY THAT IN CALIFORNIA ALONE THE CDC ESTIMATES THAT OVER A MILLION CITIZENS OF OUR STATE MAY BE CURRENTLY EXPOSED TO CHRONIC LIVER-RELATED CONDITIONS, AND THE COST TO SOCIETY AND OUR ECONOMY ARE STAGGERING. WE URGE YOU TO CONSIDER CAREFULLY THE NEEDS OF ADDRESSING THIS COMMUNITY AND ITS RELATION TO OTHER COMORBIDITIES FOR THE BENEFIT OF THE PROGRAMS THAT DEMONSTRATE REAL PROMISES IN THE FUTURE.

"WE ALSO WISH TO EXPRESS OUR INTEREST IN BEING INVOLVED AS A PARTNER IN THE EDUCATION AND PUBLIC AWARENESS OF THE PROGRESS THAT IS BEING MADE

BY CIRM AS IT RELATES TO LIVER DISEASES THAT ARE PROMINENT IN OUR COMMUNITIES. PLEASE FEEL FREE TO CONTACT US, AND WE OFFER OUR PARTICIPATION AS NEEDED TO HELP EXPEDITE THE MISSION TO FIND CURES FOR THOSE WHO ARE SUFFERING THROUGH STEM CELL RESEARCH. THANK YOU, SINCERELY, BILL REMAK."

DR. CSETE: THAT'S REALLY NICE TO HEAR. FOR THOSE OF YOU WHO DON'T KNOW ME WELL, I SPENT THE LAST 20 PLUS YEARS ON A LIVER TRANSPLANT SERVICE, SO THIS IS VERY CLOSE AND DEAR TO MY HEART. AND 2 PERCENT OF THE AMERICAN POPULATION IS HCV POSITIVE NOW.

THERE WAS NO OBVIOUS CONNECTION REALLY BETWEEN US AND CIRM, AND OUR PORTFOLIO HAS VERY LITTLE IN THE WAY OF LIVER DISEASE, BUT I CAN ASSURE OUR FRIENDS THAT THERE'S VERY INTERESTING DISEASE TEAMS BEING FORMED IN THIS AREA, AND THAT WE'RE SEEING SOME PROGRESS IN BUILDING LIVER DISEASE-RELATED RESEARCH IN STEM CELL BIOLOGY. SO THAT WAS VERY NICE TO HEAR. THANKS.

MR. SHEEHY: OTHER QUESTIONS, COMMENTS? I WOULD LIKE TO SAY I PERSONALLY TAKE A DEEP INTEREST IN HEP C SINCE I THINK, WHAT, PERHAPS 40 PERCENT OF THE HIV COMMUNITY IN SAN FRANCISCO IS HEP C CO-INFECTED. I LOSE MORE FRIENDS TO HEP C NOW THAN

I DO TO HIV. IT'S ACTUALLY MUCH HARDER TO TREAT.

MR. BROWN: I WAS JUST GOING TO PASS ALONG AN ANECDOTE. I RODE DOWN ON THE BUS FROM SANTA ROSA THIS MORNING. I HAD A LADY, BLACK LADY SAT DOWN NEXT TO ME ON THE BUS AND SAID, SOMEHOW SHE ASKED WHERE I WAS GOING AND I TOLD HER I WAS GOING TO A STEM CELL CONFERENCE THIS AFTERNOON OR A MEETING. AND SHE SAID, "OH, PLEASE TALK TO MY HUSBAND BECAUSE I'VE GOT A BAD LIVER AND I SURE NEED TO HAVE SOMETHING DONE ABOUT IT." THERE ARE PEOPLE OUT THERE THAT NEED YOUR HELP. PRESS ON. PRESS ON.

MR. SHEEHY: THANK YOU. I THINK DR. KRIEGSTEIN.

DR. KRIEGSTEIN: JUST A VERY BRIEF QUESTION. JUST ACTUALLY TWO QUESTION, ONE OF THEM HAVING TO DO WITH MY CONSTITUENTS WHO HAVE ASKED ME TO ASK THIS QUESTION, WHICH HAS TO DO WITH THE NEW FACULTY AWARDS AND WHETHER THAT WILL BE RECURRENT OR NOT.

AND THE SECOND QUESTION HAS TO DO WITH THE BOND ISSUING AND THE SCHEDULE, AND WHETHER THERE WILL BE AN INTERRUPTION OR EXACTLY WHAT THE PROSPECTS ARE FOR THE FUTURE.

DR. CSETE: WE WON'T ISSUE NEW FACULTY AWARDS THROUGH 2010 UNDER THE CURRENT CONSTRAINTS OF

ANTICIPATING A LOWER THAN WE WOULD HAVE HOPED FOR BOND FLOW TO THE AGENCY. SO I CAN'T TELL YOU WHEN THEY WOULD HAPPEN, BUT THEY WON'T HAPPEN THROUGH DECEMBER 2010.

DR. TROUNSON: I'M SORRY. IT'S CLEAR THAT THERE'S A CASH FLOW ISSUE REALLY BROUGHT ABOUT BY ISSUES IN THE STATE OF CALIFORNIA, A $40 BILLION ISSUE. AND NOW THE BUDGET HAS BEEN AGREED AND BOND SALES ARE STARTING TO TAKE PLACE, IT'S A LONG PERIOD FOR RECOVERY IN TERMS OF GETTING THE BOND MONEY TO PAY FOR SOME OF THE REALLY CRITICAL THINGS IN OUR COMMUNITY, EDUCATION, HEALTH, A LOT OF REALLY IMPORTANT INFRASTRUCTURE WHICH IS BADLY SUFFERING. MY SON'S TEACHER IS BEING BEEN PAID BY IOU'S, AND IT DOESN'T GO VERY FAR. AND SO WHAT WE DON'T WANT TO DO IS STEP IN FRONT OF THOSE COMMUNITY NEEDS.

SO THE WAY WE'VE CONSIDERED IT, AND IT'S REALLY A DECISION THAT WAS MADE BY THE ICOC, IS THAT WE OUGHT TO CONSTRUCT OUR BUDGETS FOR THE ABILITY TO PICK UP THE NORMAL STATE BONDS AT THE END OF 2010. WE WOULD HAVE SOME CONFIDENCE THAT THERE WOULD BE SUFFICIENT RECOVERY THAT BOND SALES WILL CONTINUE BECAUSE WE ARE, IN FACT, ALREADY ALLOCATED THE $3 BILLION. IT'S JUST A MATTER OF WHEN WE STEP UP.

SO IN THE INTERIM, BECAUSE WE ONLY HAVE A

HUNDRED SIXTY, LESS THAN THAT, A $130 MILLION IN THE BANK AND OUR ACCOUNT COSTS, IF WE DIDN'T GET ANY MONEY AT ALL, WE WOULD REALLY ESSENTIALLY BE UNABLE TO MEET ANY PAYMENTS AFTER, SAY, SEPTEMBER THIS YEAR. SO THE TREASURER HAS AGREED TO ENABLE US TO RAISE MONEY THROUGH PRIVATE PLACEMENT OF BONDS; THAT IS, IN SPECIAL INSTITUTIONS AND INDIVIDUALS OF HIGH NET WORTH.

AND SO WHAT WE'VE DONE IS CONSTRUCT A BUDGET THAT WOULD, FOR EXAMPLE, ACCOMMODATE AROUND $200 MILLION OF PRIVATE BOND ISSUANCE. IF WE WERE GOING TO CONTINUE AT THE RATE WHICH HAS BEEN A REALLY FAST RATE, WE WOULD PROBABLY NEED AROUND 350 MILLION. SO WE'VE SORT OF SAID WE FEEL CONFIDENT THAT WE'D BE ABLE TO RAISE AROUND 200 MILLION. THEREFORE, WE'LL HAVE TO MAKE SOME ADJUSTMENTS IN OUR PROGRAM.

SO THERE WILL BE SOME ADJUSTMENTS, AND THOSE WILL HAVE TO BE MADE, THE DECISIONS MADE BY THE ICOC. AND WE WILL BE DISCUSSING THAT WITH THEM TOMORROW. SO TOMORROW WOULD BE A BETTER DAY TO BE VERY SPECIFIC ABOUT THE WAY WE DO IT. IT'S LIKELY WE MIGHT HAVE TO SLOW DOWN SOME OF THE PROGRAM OR REDUCE, JUST FUND ONLY THE REALLY TOP PART OF THE PROGRAM IN ORDER JUST TO BECOME CASH POSITIVE. I

HAVE NO WAY OF WRITING CHECKS. THE CHECKS ARE WRITTEN REALLY BY THE COMPTROLLER. SO THERE'S NO MONEY, NO CHECKS. SO THAT'S THE SITUATION.

I THINK IT WILL BE A MINOR ADJUSTMENT, TO BE HONEST, AND SOME MINOR ADJUSTMENT WILL BE NECESSARY. THERE HAS BEEN A LOT OF PAIN AND THERE IS A LOT OF PAIN OUT THERE IN THE COMMUNITY. IT'S BEEN AWFUL. AND I THINK WE'LL PROBABLY HAVE TO TAKE A LITTLE BIT OF PAIN OURSELVES JUST TO GET THROUGH THIS PARTICULAR SECTOR OF THE ECONOMY. BUT I FEEL VERY CONFIDENT BY THE END OF 2010 WE'LL BE BACK ON TRACK AND BACK ON OUR EXPECTED PLAN. SO A MINOR BIT IRRITATING, MAYBE, REDUCTION TO ACCOMMODATE A DIP, IF YOU LIKE.

MR. SHEEHY: IF I CAN ADD, AS A BOARD MEMBER, A LOT OF THE DOOM AND GLOOM WAS HAPPENING BEFORE THE BUDGET GOT SIGNED AND BEFORE THE STIMULUS PACKAGE WAS APPROVED. BOTH OF THOSE CIRCUMSTANCES HAVE RADICALLY CHANGED THE ENVIRONMENT IN WHICH WE ARE FUNCTIONING. THE PROBLEM IS NOBODY HAS BEEN ABLE TO FIGURE OUT WHAT THAT MEANS. SO CLEARLY A SUBSTANTIAL CHUNK OF MONEY IS COMING INTO THE STATE FROM THE STIMULUS PACKAGE. AND THE FACT THAT THE BUDGET HAS BEEN SIGNED IS GOING TO ALLOW THE STATE TO START ISSUING BONDS.

AND I WOULD NOTE THAT WE HAVE BEEN APPROVED BY THE TREASURER TO ISSUE $200 MILLION THIS YEAR AND $200 MILLION NEXT YEAR IN PRIVATE PLACEMENT BONDS. WE DON'T KNOW WHAT THE MARKET IS GOING TO BE FOR THAT. ONE OF THE GREAT -- I DON'T WANT TO SAY IT'S A POSITIVE THING, BUT ONE OF THE FEATURES OF THIS DOWNTURN IS THAT INTEREST RATES ARE REALLY LOW. AND EVEN ISSUING PRIVATE PLACEMENT BONDS WHICH WOULD CARRY A PREMIUM OVER A USUAL G.O. BOND STILL PUTS US IN THE RANGE OF WHAT WE WERE TALKING ABOUT WHEN PROP 71 WAS PASSED BECAUSE THE FED IS BASICALLY GIVING AWAY MONEY NOWADAYS.

SO THE INTEREST RATES WE'RE TALKING ABOUT ARE NOT GOING TO BE ONEROUS AND FURTHER BURDEN THE PROGRAM BEYOND WHAT WE HAD ANTICIPATED WHEN PROP 71 WAS PASSED.

SO I THINK -- I GET TO VOTE ON THIS TOMORROW, SO PERSONALLY I THINK WE'VE SEEN FAR GREATER CHALLENGES AS AN AGENCY AND AS A BOARD. AND I THINK THE KEY CORE ASPECTS OF OUR PROGRAM WE'RE GOING TO KEEP MOVING FORWARD. I DON'T, FOR INSTANCE, HAVING SAT THROUGH THAT TRANSLATION ROUND, I BELIEVE WE'RE GOING TO FUND THE VERY BEST OF THAT. I TRULY DO BELIEVE THAT THE BOARD WILL MAKE THAT COMMITMENT. THE SAME THING, ASSUMING WE GET GREAT

DISEASE TEAM GRANTS, THEY MAY NOT BE ALL THAT FABULOUS, AND WE MAY DECIDE NOT TO FUND A LOT. BUT I THINK FOR THINGS THAT ARE ABSOLUTELY ESSENTIAL TO KEEPING OUR PROGRAM GOING FORWARD WE WILL FIND THE MONEY. I THINK THERE'S COMMITMENT AT THE STATE LEVEL. CLEARLY THE GOVERNOR HAS BEEN WITH US AND HAS BEEN A REAL SUPERSTAR AND SUPER HERO FOR US, AND THE TREASURER AND THE CONTROLLER AND ALL THE CONSTITUTIONAL OFFICERS, THERE'S NO WAVERING IN THEIR SUPPORT, NOR AT THE LEGISLATURE.

SO IT'S JUST GETTING THROUGH THIS, AND I KNOW FOR US IT'S IMPORTANT THAT WE COMMUNICATE, AS ALAN NOTED, THAT WE COMMUNICATE THAT WE'RE IN THIS WITH EVERYBODY ELSE THAT'S WORKING FOR THE STATE OF CALIFORNIA. I KNOW FOR LOTS OF US HERE AT UC, WE'RE SEEING THIS ON THE OTHER SIDE AND WE'RE HAVING -- I'VE SEEN PEOPLE LEAVE THEIR JOBS IN MY UNIT. AND THIS IS PAINFUL FOR US. BUT I THINK THAT WE'RE GOING TO COME OUT OF THIS, AND I DON'T THINK WE'RE GOING TO SEE SEVERE ATTENUATION OF PROGRAM. I THINK WE'RE GOING TO SEE SOME TRIMMING AROUND THE EDGES. WE'RE NOT GOING TO BE ABLE TO GO DOWN AS FAR. WE TYPICALLY HAVE THREE CATEGORIES, AND THE TOP ONE IS THE FUNDABLE CATEGORY. I THINK THOSE ARE PROBABLY GOING TO BE FOR THE MOST PART OKAY. I THINK THAT

SECOND CATEGORY, FUND IF FUNDS ARE AVAILABLE, IT'S GOING TO BE TOUGH, BUT LUCKILY THE WAY DR. CSETE HAS THIS ARRANGED, WE CAN COME BACK NEXT YEAR, AND NEXT YEAR WE SHOULD BE FINE ACTUALLY.

AS HAS BEEN NOTED, WERE FULLY AUTHORIZED FOR THE WHOLE 3 BILLION. IN TERMS OF THE PRIVATE PLACEMENT, IT IS IMPORTANT TO NOTE THAT INVESTORS LOOK AT CALIFORNIA BONDS AS BEING VERY SAFE BECAUSE THE STATE HAS TO PAY THEM SECOND AFTER PAYING FOR SCHOOL, SO CALIFORNIA HAS TO PAY ITS DEBT. SO IT'S NOT VERY RISKY DEBT. IT'S NOT LIKE SOME OF THE THINGS THAT ARE BEING TOSSED AROUND LIKE THESE CDO'S OR OTHER THINGS THAT HAVE GONE DOWN THE PIKE.

SO I DON'T WANT THE SCIENTIFIC COMMUNITY TO THINK THAT WE'RE NOT GOING TO BE IN BUSINESS BECAUSE WE ARE. AND COME HELL OR HIGH WATER, WE'VE BEEN THROUGH A LOT WORSE, LET ME TELL YOU. SO WE'LL BE THERE AND WE'LL BE HERE.

ANY OTHER -- I DON'T MIND FINISHING UP EARLY, BUT PEOPLE HAVE ANY KIND -- ANY ADDITIONAL INPUT?

MR. LUBIN: I THINK THIS HAS BEEN A WONDERFUL DISCUSSION. I JUST WANTED TO COMMENT ON HOW THE REVIEWERS ARE INSTRUCTED TO REVIEW APPLICATIONS GIVEN WHAT NIH -- IF YOU LOOK AT HEART,

LUNG, AND BLOOD STIMULUS AWARDS, ABOUT 75 PERCENT OF THEM ARE IPS RELATED. IPS IS IN THEM. SO HOW ARE THE REVIEWERS GOING TO BE IDENTIFYING SOMETHING THAT'S UNIQUE FOR CALIFORNIA? SEEMS LIKE A CHALLENGE. I KNOW YOU'VE BEEN STRUGGLING WITH THIS, AND I THINK THAT'S IMPORTANT FOR US WHO ARE SUBMITTING APPLICATIONS.

DR. CSETE: SO I LOVE YOU SCIENTISTS. WE MAKE OUR REVIEW CRITERIA CLEAR IN THE RFA. AND THE CRITERIA THAT ARE IN THE RFA ARE NO DIFFERENT THAN THE CRITERIA THAT ARE GIVEN TO THE REVIEWERS. SO NOT A SECRET AT ALL. AND AS I SAID, ONE OF THEM HAS ALWAYS BEEN THE UNIQUE ABILITY OF CIRM TO FUND THIS PARTICULAR PROJECT COMPARED TO THE AVAILABILITY OF FUNDS IN OTHER AGENCIES. SO IT'S ONE OF MANY CRITERIA, BUT THEY'RE ALL THERE FOR YOU.

DR. TROUNSON: JUST ONE THING. YOU KNOW, I TAKE IT THAT THE POINT YOU'RE MAKING IS THAT IT WOULD BE A GOOD IDEA THAT WE ACTUALLY KNEW WHAT EACH OTHER WERE DOING IN TERMS OF THOSE AGENCIES. AND SO I HOPE THAT'S THE KIND OF ARRANGEMENT WE'LL COME TO, THAT WE WILL HAVE AN UNDERSTANDING OF WHAT THE PRIORITIES OF THE NIH ARE AND THAT WE CAN DO THESE THINGS IN A MUCH MORE INTEGRATED WAY OR PARTNERSHIP MANNER. I THINK THERE'S SO MANY NEW IDEAS COMING AT

THE MOMENT, TO BE HONEST, THAT THE WORLD IS AWASH WITH SOME REALLY INNOVATIVE SCIENCE. AND CLEARLY I KNOW THAT YOU'RE INVOLVED WITH SOME VERY INTERESTING NEW WORK. SO I WOULDN'T BE AFRAID OF INNOVATION THAT MIGHT BE THE NEXT PLATFORM.

IPS CELLS ARE JUST MAGNIFICENT AND FANTASTIC AS EMBRYONIC STEM CELLS HAVE BEEN AND STILL ARE, BUT THERE ARE ALSO TREMENDOUS OPPORTUNITIES STILL THERE. I MEAN REALLY IN MY OWN FEELING AS A SCIENTIST, WE'RE STILL SCRATCHING THE SURFACE OF THE OPPORTUNITIES. SO WE'LL BE LOOKING FOR THOSE DIAMONDS AMONGST ALL OF THOSE IDEAS THAT COME FORWARD BECAUSE THERE MAY BE SOMETHING HERE THAT CHANGES THE PARADIGM YET AGAIN.

AND THERE MAY BE, FOR EXAMPLE, VERY AVAILABLE TISSUE THAT CAN BE USED IMMEDIATELY FOR AN APPROPRIATE APPLICATION THAT WE HADN'T THOUGHT OF. SO ALL OF THESE THINGS REMAIN POSSIBLE. WE WANT TO ENCOURAGE THAT. WE WILL LOOK TO WHERE WE CAN BUILD ON WHAT WE'VE BEEN DOING, BUT WE'LL LOOK FOR THE GENUINE OPPORTUNITIES, AND THEN WE'LL BE ABLE TO SAY, I THINK, TO EVERYBODY, HOPEFULLY WITHIN THE NEXT 12 MONTHS, THAT WE HAVE SOME AGREEMENTS WITH NIH TO JOINTLY EXPLORE SOME OF THESE AREAS TOGETHER SO WE EACH KNOW WHAT OUR PARTICULAR PERSPECTIVE IS.

AND JOINT ARRANGEMENTS PARTICULARLY, AS YOU KNOW, WITH OTHER GROUPS CAN BE VERY, VERY PROFITABLE IN TERMS OF OUTCOME. SO WE'RE HOPEFUL THAT THAT WILL ALL CONTINUE, AND THAT'S NOT IN ANY WAY TO SAY THAT THE SCIENTIST WORKING IN HIS OWN LAB IN SOME ROUNDABOUT PLACE WHO COMES THROUGH WITH A BRILLIANT IDEA, THEY'RE TO BE CHERISHED, CHERISHED BY INSTITUTIONS, BUT ALSO BY PEOPLE LIKE US. AND THE QUALITY, THE QUALITY OF SOME OF THOSE IDEAS, IF THEY CAN BE DRAWN OUT, WILL MAKE A DIFFERENCE.

SO I HOPE YOU UNDERSTAND THAT WE'RE GOING TO DO OUR BEST TO UNDERSTAND WHAT EACH IS DOING, BUT TO BE AWARE OF THE CREATIVE ASPECT OF RESEARCH AND YET THE OPPORTUNITY TO GO TO THE CLINIC. I DON'T THINK WE CAN PUT THAT ASIDE IN ANY SENSE, AND I DON'T FEEL THAT ANYONE SAID THAT. I THINK WHAT WE'RE TALKING ABOUT IS WITH A GREAT DEAL OF CARE OR AS MUCH CARE AS POSSIBLE. BUT THERE ARE PATIENTS OUT THERE WHO DESPERATELY NEED SOME ALTERNATIVE. AND IF WE CAN GET THEM A TREATMENT, WHICH IS NOT NECESSARILY A CURE, BUT IMPROVES THEIR QUALITY OF LIFE, I THINK IT WOULD BE A REWARDING EXPERIENCE TO GET THERE.

DR. CSETE: I KNOW THAT THERE'S ALSO A LOT OF ANGST IN THE COMMUNITY ABOUT THIS FIRST ROUND OF

DISEASE TEAMS. AND NOTHING HAS CHANGED AT NIH YET. AND THEY'RE NOT AN AGENCY KNOWN FOR NIMBLENESS NECESSARILY, SO IT'S GOING TO TAKE A FAIR AMOUNT OF TIME FOR THEM TO GET PROGRAMS IN PLACE THAT I THINK ARE REALLY ANYWHERE CLOSE TO THE KINDS OF PROGRAMS WE'VE HAD.

I GO TO STUDY SECTION VERY FRUSTRATED AT THE KIND OF PROGRAMS THAT HAVE BEEN PUT FORTH IN STEM CELL BIOLOGY THERE BECAUSE THEY'VE BEEN REALLY SO CAREFUL ABOUT A POLITICAL LINE, AND WE HAVEN'T HAD TO DO THAT, SO I THINK WE ARE STILL IN A UNIQUE POSITION.

MR. SHEEHY: ANY OTHER QUESTIONS OR COMMENTS? I WANT TO THANK EVERYONE FOR COMING TODAY AND FOR YOUR INPUT. AND I ALSO WANT TO THANK THE GLADSTONE, WHICH I SHOULD HAVE DONE AT THE BEGINNING. I FEEL LIKE I'M HOME WHEN I'M HERE. THEY'RE SUCH A FABULOUS PLACE AND INCREDIBLE SCIENCE. SUCH A BEAUTIFUL SPACE TOO, SO I ALWAYS LOVE COMING HERE.

SO THANK YOU VERY MUCH. AND I THINK, WHAT, WE'RE GOING TO BE BRINGING THIS AROUND PROBABLY FOR APRIL AT THE ICOC, THE ACTUAL PLAN.

(THE MEETING WAS THEN ADJOURNED AT 02:43 P.M.)

REPORTER'S CERTIFICATE

I, BETH C. DRAIN, A CERTIFIED SHORTHAND REPORTER IN AND FOR THE STATE OF CALIFORNIA, HEREBY CERTIFY THAT THE FOREGOING TRANSCRIPT OF THE PROCEEDINGS BEFORE THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF A PUBLIC COMMENT SESSION REGARDNG CIRM'S STRATEGIC PLAN WAS HELD AT THE LOCATION INDICATED BELOW

THE GLADSTONE INSTITUTE
1650 OWENS STREET
SAN FRANCISCO, CALIFORNIA
ON
WEDNESDAY, MARCH 11, 2009

WAS HELD AS HEREIN APPEARS AND THAT THIS IS THE ORIGINAL TRANSCRIPT THEREOF AND THAT THE STATEMENTS THAT APPEAR IN THIS TRANSCRIPT WERE REPORTED STENOGRAPHICALLY BY ME AND TRANSCRIBED BY ME. I ALSO CERTIFY THAT THIS TRANSCRIPT IS A TRUE AND ACCURATE RECORD OF THE PROCEEDING.

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